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BJA

British Journal of Anaesthesia

International Journal of Anaesthesia

Volume 88 Number 1 January 2002

Editor-in-chief: Jennifer M. Hunter

- Extreme value theory and breathing patterns
- *On-line* monitoring of stroke volume
- Anaphylactoid reactions to contrast media

Journal of The Royal College of Anaesthetists

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Prolonged release oxycodone hydrochloride tablet

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FOR MODERATE TO SEVERE PAIN IN MALIGNANCY AND POST-OPERATIVE PATIENTS

PRESCRIBING INFORMATION OxyContin®▼ 10 mg, 20 mg, 40 mg, 80 mg tablets United Kingdom **Presentation** Film-coated, prolonged release tablets containing oxycodone hydrochloride, marked OC on one side and the strength of oxycodone hydrochloride on the other. The 10 mg tablets are white and contain 10 mg of oxycodone hydrochloride. The 20 mg tablets are pink and contain 20 mg of oxycodone hydrochloride. The 40 mg tablets are yellow and contain 40 mg of oxycodone hydrochloride. The 80 mg tablets are green and contain 80 mg of oxycodone hydrochloride. **Indications** For the treatment of moderate to severe pain in patients with cancer and post-operative pain. **Dosage and administration** OxyContin tablets must be swallowed whole, and not chewed. *Elderly and adults over 18 years:* OxyContin tablets should be taken at 12-hourly intervals. The dosage is dependent on the severity of the pain, and the patient's previous history of analgesic requirements. The usual starting dose for opioid naïve patients or patients presenting with severe pain uncontrolled by weaker opioids is 10 mg, 12-hourly. If higher doses are necessary, increases should be made, where possible in 25% - 50% increments. Patients transferring from morphine should have the daily dose based on the following ratio: 10 mg oral oxycodone is equivalent to 20 mg oral morphine. For most patients the maximum dose of OxyContin tablets is 200 mg, 12-hourly. However, a few patients may require higher doses. Doses in excess of 1000 mg have been reported. *Children under 18 years:* Not recommended. **Contra-indications** Respiratory depression, head injury, paralytic ileus, acute abdomen, delayed gastric emptying, chronic obstructive airways disease, chronic bronchial asthma, hypercarbia, known oxycodone sensitivity, moderate to severe hepatic impairment, severe renal impairment, chronic constipation, concurrent administration of monoamine oxidase inhibitors or within 2 weeks of discontinuation of their use. Not recommended for pre-operative use or for the first 24 hours post-operatively. Pregnancy. **Precautions and warnings** A reduction in dosage may be advisable in hypothyroidism. Use with caution in opioid dependent patients and in patients with raised intracranial pressure, hypotension, hypovolaemia, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, prostatic hypertrophy, adrenocortical insufficiency, acute alcoholism, chronic renal and hepatic disease, and debilitated patients. OxyContin tablets should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, OxyContin tablets should be discontinued immediately. Patients who are to undergo cordotomy or other pain relieving surgical procedures should not receive OxyContin tablets for 24 hours before surgery. If further treatment with OxyContin tablets is then indicated the dosage should be adjusted to the new post-operative requirement. OxyContin tablets should be used with caution following abdominal surgery, as opioids are known to impair intestinal motility and should not be used until the physician is assured of normal bowel function. **Pregnancy and lactation** Not recommended. Oxycodone is secreted in breast milk and may cause respiratory depression in the newborn. OxyContin tablets should, therefore, not be used in breast-feeding mothers. **Side-effects** Adverse drug reactions are typical of full opioid agonists. Tolerance and dependence may occur. The most common adverse drug reactions seen during therapy are constipation (which may be prevented with an appropriate laxative), nausea, dizziness, pruritus, urticaria, vomiting, headache, dry mouth, sweating, drowsiness and asthenia. If nausea and vomiting are troublesome, oxycodone may be combined with an antiemetic. Occasional adverse reactions are anorexia, nervousness, insomnia, fever, confusion, diarrhoea, abdominal pain, vasodilation, dyspepsia, paraesthesia, rash, anxiety, euphoria, depression, dyspnoea, postural hypotension, chills, abnormal dreams, thought abnormalities, hiccups. Vertigo, twitching, gastritis, disorientation, facial flushing, mood changes, palpitations, hallucinations, bronchospasm and colic may occur in a few patients. Micturition may be difficult and there may be biliary or ureteric spasm. Overdose may produce respiratory depression. Rarely, clinically relevant reductions in blood pressure and heart rate have been observed. **Legal category** CD (Sch2) POM. **Package quantities and price** Blister packs of 56 tablet 10 mg – £21.43. 20 mg – £42.86. 40 mg – £85.7 80 mg – £171.46. **Marketing Authorisatio numbers** PL 16950/0097-0100. **Marketin Authorisation holder** Napp Pharmaceutical Limited, Cambridge Science Park, Milton Roa Cambridge. CB4 0GW. UK. Tel: 01223 42444 Member of the Napp Pharmaceutical Group. Further information is available from Napp Pharmaceuticals Limited. **Date of preparation** July 2001. ® OXYCONTIN and the NAPP device are Registered Trade Marks. © Napp Pharmaceuticals Limited 2001. European Patent (UK) 0 253 104. European Patent (UK) 0 576 643. European Patent Application No. 96102992.3.

Date of preparation September 2001.

A world leader NAPP in pain control

BJA
International Journal of Anaesthesia
Volume 88 Number 1 January 2002

5?

EDITORIALS

1 I. The sitting position in neurosurgery—not yet obsolete!
I. E. Leonard and A. J. Cunningham
4 II. Oxygen and elective Caesarean section
S. K. Backe and G. Lyons
6 III. Blood transfusion in critical illness
L. McCrossan and G. Masterson
9 IV. Airway management in the emergency department
J. Nolan and M. Clancy

EDITORIAL NOTE

11 A freely accessible *BJA* archive
J. M. Hunter

CLINICAL INVESTIGATIONS:

12 The sitting position for neurosurgery in children: a review of 16 years' experience
E. A. Harrison, A. Mackersie, A. McEwan and E. Facer
18 Effects of high inspired oxygen fraction during elective Caesarean section under spinal anaesthesia on maternal and fetal oxygenation and lipid peroxidation
K. S. Khaw, C. C. Wang, W. D. Ngan Kee, C. P. Pang and M. S. Rogers
24 Model-based administration of inhalation anaesthesia. 3. Validating the system model
J. G. C. Lerou and L. H. D. J. Booij
38 Predictive performance of a physiological model for enflurane closed-circuit anaesthesia: effects of continuous cardiac output measurements and age-related solubility data
P. M. Vermeulen, C. J. Kalkman, R. Dirksen, J. T. A. Knape, K. G. M. Moons and G. F. Borm
46 Fresh gas flow is not the only determinant of volatile agent consumption: a multicentre study of low-flow anaesthesia
J. F. Coetzee and L. J. Stewart
56 Intrinsic positive end-expiratory pressure during one-lung ventilation of patients with pulmonary hyperinflation. Influence of low respiratory rate with unchanged minute volume
L. L. Szegedi, L. Barvais, Y. Sokolow, J. C. Yernault and A. A. d'Hollander
61 Extreme value theory applied to postoperative breathing patterns
Y. P. Leong, J. W. Sleigh and J. M. Torrance
65 Randomized controlled trial to investigate influence of the fluid challenge on duration of hospital stay and perioperative morbidity in patients with hip fractures
R. Venn, A. Steele, P. Richardson, J. Poloniecki, M. Grounds and P. Newman
72 Double-blind, placebo-controlled analgesic study of ibuprofen or rofecoxib in combination with paracetamol for tonsillectomy in children
A. E. Pickering, H. S. Bridge, J. Nolan and P. A. Stoddart

LABORATORY INVESTIGATIONS

78 Effects of intracoronary calcium chloride on regional oxygen balance and mechanical function in normal and stunned myocardium in dogs
K. Y. Yoo, J. U. Lee, S. H. Kwak, W. M. Im, C. Y. Jeong, S. S. Chung, M. H. Yoon, S. W. Jeong and J. T. Park
87 Naloxone prevents increased atrial natriuretic peptide release during regional myocardial ischaemia and stunning in awake dogs
T. P. Weber, C. Raufhake, M. A. Große Hartlage, N. Rolf, J. Stypmann, H. Van Aken, E. Berendes and A. Meißner
94 Concurrent ketamine and alfentanil administration: pharmacokinetic considerations
S. R. Edwards, C. F. Minto and L. E. Mather

REVIEW ARTICLE

101 Modulation of β-adrenergic receptor subtype activities in perioperative medicine: mechanisms and sites of action
M. Zaugg, M. C. Schaub, T. Pasch and D. R. Spahn

SHORT COMMUNICATIONS

124 Optimizing fluid therapy in mechanically ventilated patients after cardiac surgery by on-line monitoring of left ventricular stroke volume variations. Comparison with aortic systolic pressure variations
D. A. Reuter, T. W. Felbinger, E. Kilger, C. Schmidt, P. Lamm and A. E. Goetz
127 Reliability of epigastric auscultation to detect gastric insufflation
J. Brimacombe, C. Keller, S. Kurian and J. Myles
129 Deep topical fornix nerve block versus peribulbar block in one-step adjustable-suture horizontal strabismus surgery
E. S. Aziz and M. Rageh

CASE REPORTS

133 Cardiac arrest after administration of Omnipaque radiocontrast medium during endoluminal repair of abdominal aortic aneurysm
V. Brown, B. Brandner, J. Brook and M. Adiseshiah
136 Paradoxical air embolism during hepatic resection
S. Y. Lee, B. I. W. Choi, J. S. Kim and K. S. Park
139 Skin necrosis following injection of non-steroidal anti-inflammatory drug
A. M. McGee and P. M. Davison
141 Recurrent neurological symptoms in a patient following repeat combined spinal and epidural anaesthesia
S. Sakura, K. Toyota, K. Doi and Y. Saito
144 Loss of the guide wire: mishap or blunder?
W. Schummer, C. Schummer, E. Gaser and R. Bartunek

147 CORRESPONDENCE

155 BOOK REVIEWS

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otes coagulation. Coagulation promotes inflamm
flammation promotes coagulation. Coagulation p
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We interrupt this to bring you a very important message:
By the time you've read this, someone will have died from **sepsis.**

Recent analyses conducted by ICNARC (the Intensive Care National Audit & Research Centre) on data collected from 92 adult general ICUs[†] have shown that the prevalence of severe sepsis[‡] during the first 24 hours in the ICU is 27.7%[§1]. In England and Wales (excluding Northern Ireland and Scotland), this figure potentially represents a prevalence of 21,033[§1] severe sepsis cases during the first 24 hours in the ICU out of a total adult general ICU caseload of 73,203[§1].

Severe sepsis is a major cause of morbidity and mortality. In adults, severe sepsis has been associated with mortality rates ranging from 28% to 50%[2] and these rates have remained unchanged for several decades. For the 92 adult general ICUs included in the Case Mix Programme Database, the associated overall hospital mortality for severe sepsis in England, Wales and Northern Ireland is 44.7%[§1].

Lilly Critical Care continues to invest extensively in research to find better ways to manage sepsis.

References
1. Eli Lilly and Company. Data on file. Source of data: The Intensive Care National Audit & Research Centre. **2.** Natanson C et al. *Crit Care Med* 1998;26:1927–31.

† throughout England, Wales and Northern Ireland; ‡ defined as sepsis associated with acute organ dysfunction; § these figures do not include cases of severe sepsis that occur either on wards or after the first 24 hours in the ICU.

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Answers That Matter.

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KILL

VIOXX®ACUTE ▼
(rofecoxib)
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PRESENTATION

Tablets: 25 mg and 50 mg tablets each containing 25 mg or 50 mg of rofecoxib.

USES

Relief of acute pain. Treatment of primary dysmenorrhoea

DOSAGE AND ADMINISTRATION

The recommended adult initial dose is 50 mg once daily, orally, with or without food. Subsequent doses should be 25 or 50 mg once daily. The maximum recommended daily dose is 50 mg. Use for the acute symptomatic period only. *Elderly:* It is prudent to use the lowest recommended dose and exercise caution in the treatment of elderly patients. *Renal insufficiency:* no dosage adjustment is necessary for patients with creatinine clearance 30-80 ml/min. *Children:* not indicated.

CONTRA-INDICATIONS

Hypersensitivity to any excipient of this product. Active peptic ulceration or gastro-intestinal (GI) bleeding. Hepatic dysfunction. Estimated creatinine clearance <30 ml/min. Patients who have developed asthma, acute rhinitis, nasal polyps, angioneurotic oedema or urticaria after aspirin or other NSAIDs. Third trimester of pregnancy and lactation. Inflammatory bowel disease. Severe congestive heart failure.

PRECAUTIONS

Consider monitoring renal function in patients with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis. Use caution when initiating treatment in patients with considerable dehydration. Rehydrate patients prior to starting therapy with rofecoxib. Consider the possibility of fluid retention and exercise caution when rofecoxib is used in patients with pre-existing oedema, a history of heart failure, left ventricular dysfunction or hypertension. Maintain appropriate supervision when treating the elderly or patients with renal, hepatic or cardiac dysfunction with rofecoxib. Rofecoxib may mask fever. Use of rofecoxib is not recommended in women attempting to conceive. In clinical studies, some osteoarthritis (OA) patients treated with rofecoxib developed perforations, ulcers or bleeds (PUBs). Patients with a prior history of a PUB and patients greater than 65 years of age appeared to be at a higher risk for a PUB. At chronic daily doses higher than 25 mg, the risks of gastro-intestinal symptoms, oedema or hypertension are increased. Elevations of ALT and/or AST (≥ 3 times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with rofecoxib. Any patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated. *Interactions (pharmacodynamic): Warfarin:* closely monitor the prothrombin time INR when therapy with rofecoxib is initiated or changed in patients receiving warfarin or similar agents, particularly in the first few days. *ACE-inhibitors:* administration of 25 mg daily of rofecoxib with benazepril, 10 mg to 40 mg daily for four weeks to patients with hypertension was associated with a small attenuation of the antihypertensive effect compared to the ACE inhibitor alone. This should be considered in patients taking rofecoxib concomitantly with ACE inhibitors. *Beta-blockers and diuretics:* concomitant use of NSAIDS may reduce the antihypertensive efficacy of beta-blockers and diuretics and the other effects of diuretics. *Aspirin:* at steady state, rofecoxib 50 mg once daily had no effect on the anti-platelet activity of low-dose (81 mg once daily) aspirin. Avoid concomitant administration of rofecoxib with higher doses of aspirin or other NSAIDS. *Cyclosporin/tacrolimus:* monitor renal function when rofecoxib and either cyclosporin or tacrolimus is used in combination. *Interactions (pharmac[illegible]tic): Lithium:* NSAIDS may increase plasma lithium concentrations. *Methotrexate:* consider adequate monitoring for methotrexate-related toxicity when rofecoxib and methotrexate are administered concomitantly. *CYP1A2 substrates:* exercise care with concomitant administration of rofecoxib with drugs primarily metabolised by CYP1A2 (e.g. theophylline, amitriptyline, tacrine and zileuton) *Midazolam:* a modest 30% reduction of the AUC of midazolam was seen with rofecoxib 25 mg daily, most likely due to increased first pass metabolism through induction of intestinal CYP3A4 activity by rofecoxib. *CYP3A4 substrates:* in spite of a modest induction of intestinal CYP3A4 activity, the pharmacokinetics of drugs metabolised primarily by CYP3A4 are not expected to be affected to a clinically significant extent. However exercise care when co-prescribing substrates of CYP3A4 with

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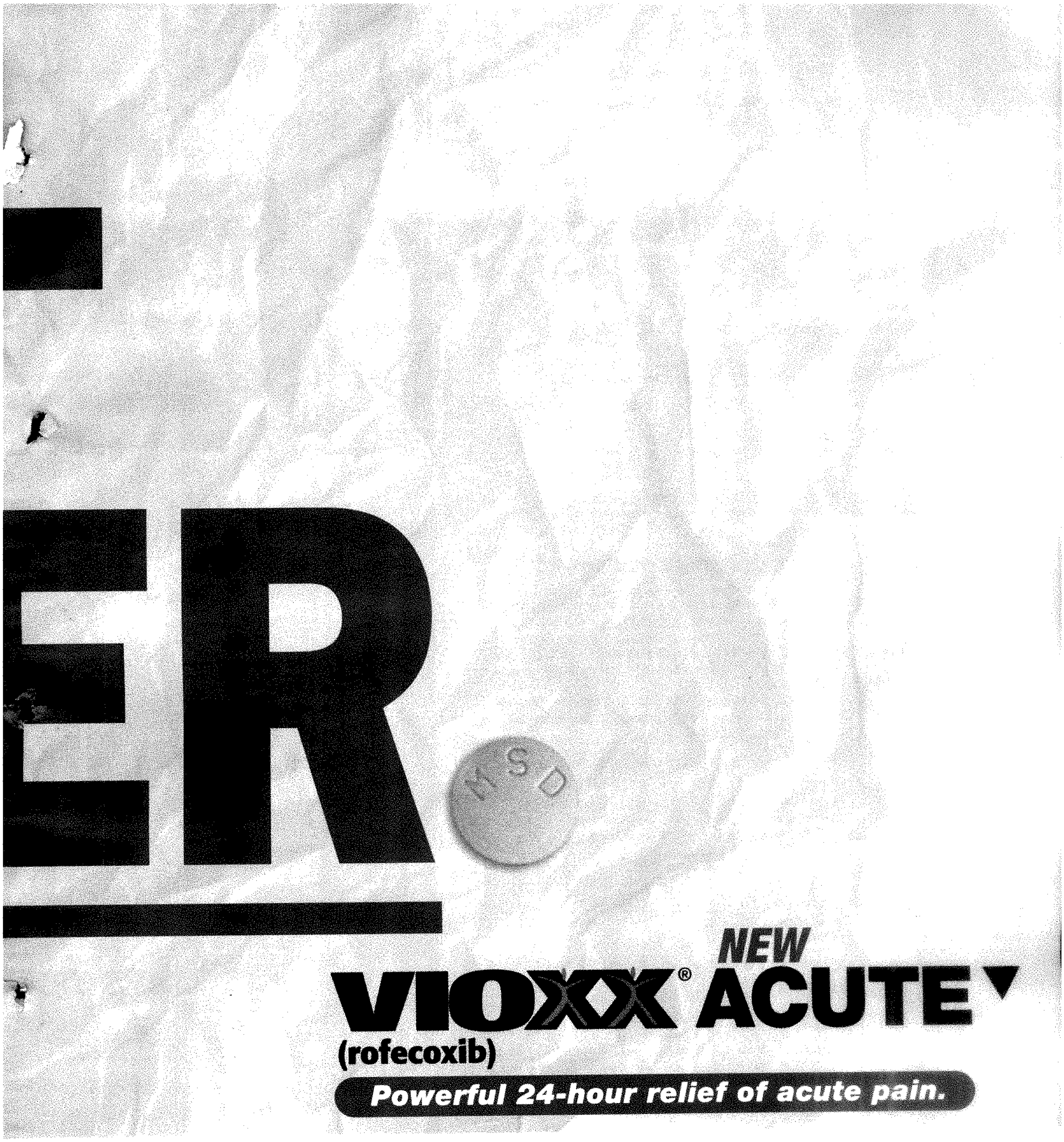

ecoxib. *Rifampicin:* co-administration of rofecoxib with rifampicin, a potent inducer of CYP ymes, produced an approximate 50% decrease in rofecoxib plasma concentrations. Therefore, isider the highest dose when rofecoxib is used with potent inducers of hepatic metabolism. Based *in vitro* data, rofecoxib is not expected to inhibit cytochromes P450, 2C9, 2C19, 2D6 or 2E1. *gnancy:* Do not use in the last trimester of pregnancy, because like other prostaglandin synthesis ibitors rofecoxib may cause uterine inertia and premature closure of the ductus arteriosus. Rofecoxib uld not be used during the first two trimesters of pregnancy unless the benefit to the patient weighs the risk to the foetus. *Lactation:* contra-indicated.

DE EFFECTS

e following drug-related undesirable effects were reported at an incidence greater than 1% and ater than placebo in analgesia clinical studies in patients treated with rofecoxib 50 mg or 25 mg 1 to 5 days: dizziness, diarrhoea, diaphoresis, dyspepsia. The following drug-related undesirable ects were reported at an incidence greater than placebo in osteoarthritis clinical studies in patients ated with rofecoxib 12.5 mg or 25 mg for up to six months, or in post-marketing experience. *ommon (≥1/100, <1/10); Uncommon (≥1/1000, <1/100); Rare (≥1/10,000, <1/1000); Very e (<1/10,000) and isolated cases]*

dy as a whole/site unspecified: *Common:* oedema/fluid retention, abdominal pain, dizziness. *common:* asthenia/fatigue, abdominal distension, chest pain. *Very rare:* hypersensitivity reactions, luding angioedema, urticaria and anaphylactic/anaphylactoid reactions. ***Blood and the lymphatic system disorders:*** *Common:* haematocrit decreased. *Uncommon:* haemoglobin decreased, erythrocytes decreased, leukocytes decreased. *Very rare:* thrombocytopenia. ***Cardiovascular system:*** *Common:* hypertension. *Very rare:* congestive heart failure. ***Digestive system:*** *Common:* heartburn, epigastric discomfort, diarrhoea, nausea, dyspepsia. *Uncommon:* constipation, oral ulcer, vomiting, digestive gas symptoms, acid reflux. *Rare:* peptic ulcers, gastro-intestinal perforation and bleeding (mainly in elderly patients), gastritis. ***Hepatobiliary disorders:*** *Common:* alanine aminotransferase increased, aspartate aminotransferase increased. *Uncommon:* alkaline phosphatase increased. *Isolated cases:* hepatotoxicity including hepatitis and jaundice. ***Eyes, ears, nose and throat:*** *Uncommon:* tinnitus. *Very rare:* blurred vision. ***Metabolism and nutrition:*** *Uncommon:* weight gain. ***Musculoskeletal:*** *Uncommon:* muscular cramp. ***Nervous system:*** *Common:* headache. *Uncommon:* insomnia, somnolence, vertigo. *Very rare:* paraesthesia. *Isolated cases:* aseptic meningitis. ***Psychiatric disorder:*** *Uncommon:* depression, mental acuity decreased. *Very rare:* confusion, hallucinations. ***Respiratory system:*** *Uncommon:* dyspnoea. *Very rare:* bronchospasm. ***Urogenital:*** *Uncommon:* BUN increased, serum creatinine increased, proteinuria. *Very rare:* renal insufficiency, including renal failure, usually reversible upon discontinuation of therapy. ***Skin and skin appendages:*** *Common:* pruritus. *Uncommon:* rash, atopic dermatitis. *Very rare:* alopecia. *Isolated cases:* cutaneo-mucosal adverse effects and severe skin reactions including Stevens-Johnson Syndrome. In clinical studies, the undesirable effects profile was similar in patients treated with rofecoxib for one year or longer. The following serious adverse effects have been reported in association with the use of NSAIDs and cannot be ruled out for rofecoxib: nephrotoxicity including interstitial nephritis and nephrotic syndrome; hepatotoxicity including hepatic failure.

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25 mg: packs of 14 tablets: £10.79. 50 mg: packs of 7 tablets: £5.39

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Epoetin alfa solution presented as 1,000 IU/0.5 ml, 2,000 IU/0.5 ml, 3,000 IU/0.3 ml, 4,000 IU/0.4 ml and 10,000 IU/ml in pre-filled syringes and 1,000 IU/0.5 ml, 2,000 IU/ml, 4,000 IU/ml and 10,000 IU/ml in vials. For subcutaneous (SC) injection.

Uses:
To increase autologous blood yield from adult patients in a predonation (ABD) programme (treat only patients with moderate anaemia if blood saving procedures not available or insufficient, when scheduled major elective surgery requires large blood volume). To reduce exposure to allogeneic blood tranfusions prior to major elective orthopaedic surgery (restrict use to patients with moderate anaemia, not having ABD, with expected moderate blood loss).

Dosage and administration:
ABD: IV route. Mildly anaemic patients (haematocrit 33-39%) requiring predeposit of ≥4 blood units: 600 IU/kg 2 times weekly for 3 weeks after the blood donation procedure, prior to surgery. Iron supplementation required.

Elective orthopaedic surgery: SC route. 600 IU/kg weekly three weeks prior to surgery and on surgery day. Where surgery lead time <3 weeks, 300 IU/kg ten consecutive days prior to surgery, on surgery day and for 4 days immediately after. Stop treatment if Hb level reaches 15 g/dl. Iron supplementation required.

Contra-indications:
Uncontrolled hypertension. All ABD programmes' contra-indications. Component hypersensitivity. Prior to major elective orthopaedic surgery in patients (not participating in an ABD programme) with severe coronary, peripheral arterial, carotid or cerebral vascular disease, including those with recent myocardial infarction or cerebral vascular accident. Patients who cannot receive adequate antithrombotic prophylaxis.

Warnings and precautions:
Closely monitor blood pressure. Epilepsy and chronic liver failure--use with caution. Consider and treat all other causes of anaemia before starting EPREX. Mostly, serum ferritin falls simultaneously with packed cell volume rise. Assure adequate iron stores to ensure optimum EPREX response. Monitor platelet count regularly during first 8 weeks. Epoetin alfa cannot be excluded as possible growth factor for any tumour type. Respect special warnings associated with ABD programme. Prior to elective orthopaedic surgery--establish anaemia cause and determine thromboembolic risk/benefit. Give adequate antithrombotic prophylaxis. If Hb >13 g/dl do not use; increased risk of thrombotic vascular events.

Use in pregnancy and lactation only if potential benefit outweighs potential risk to foetus or baby.

Side effects:
Nonspecific skin rashes and flu-like symptoms. Increased risk of thrombotic/vascular events where Hb >13 g/dl prior to elective orthopaedic surgery.

Overdosage:
High therapeutic margin. Phlebotomy may be performed if Hb too high.

Interactions:
Do not administer with other drug solutions. Potential cyclosporin interaction. No interaction evidence with G-CSF or GM-CSF.

Pharmaceutical precautions:
Store at 2 to 8°C. Do not freeze or shake. Protect from light. Unpreserved product. Administer only one dose per vial or syringe.

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References:

1. Stowell CP, Chandler H, Jové M, Guilfoyle M, Wacholtz MC. *Orthopedics.* 1999;22(suppl 1):s105-s112.
2. de Andrade JR, Jove M, Landon G, Frei D, Guilfoyle M, Young DC. *Am J Orthop.* 1996;25:533-542.
3. Keating EM, Ranawat CS, Cats-Baril W. *Orthopedics.* 1999;22(suppl 1):s119-s128.

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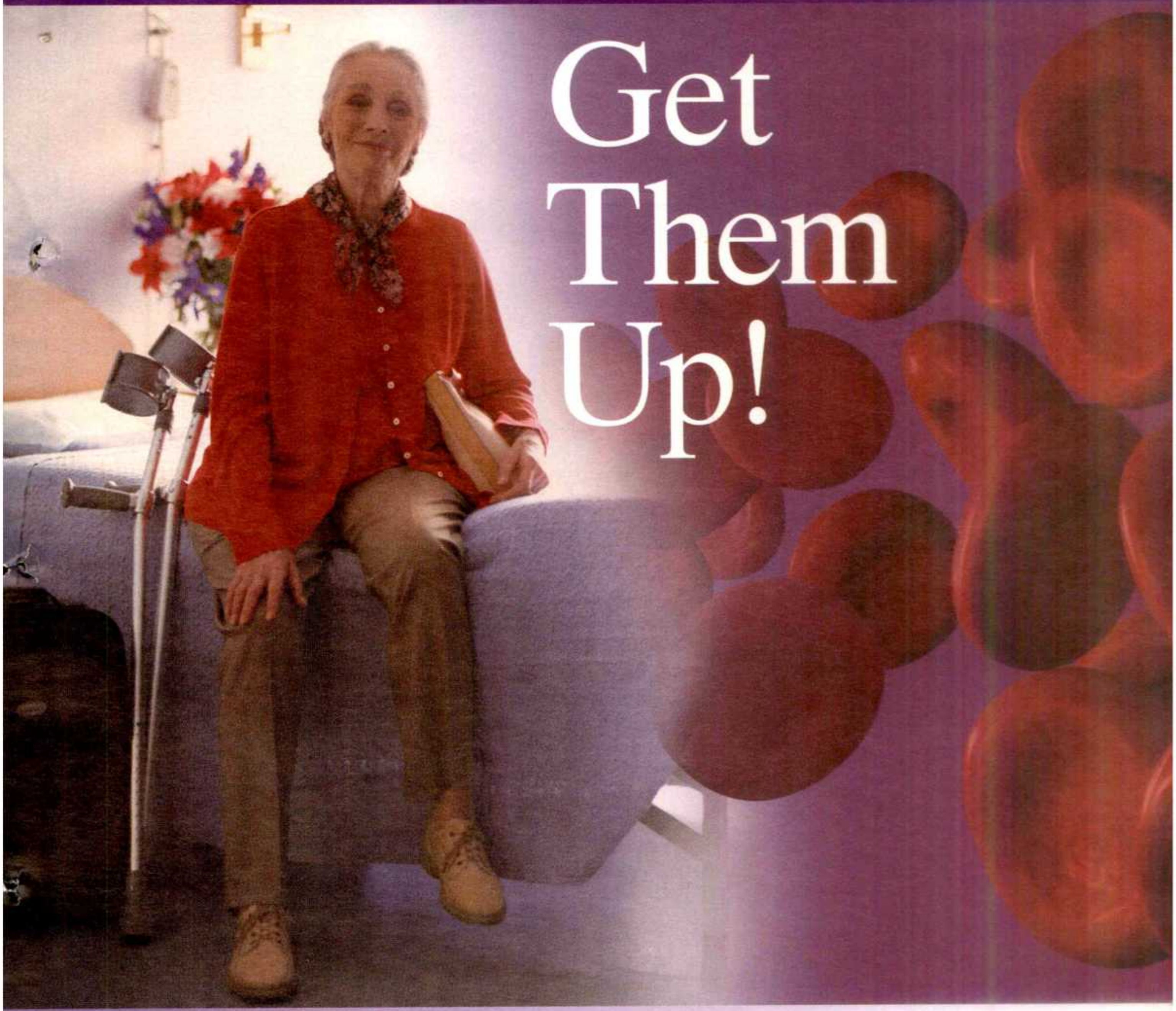

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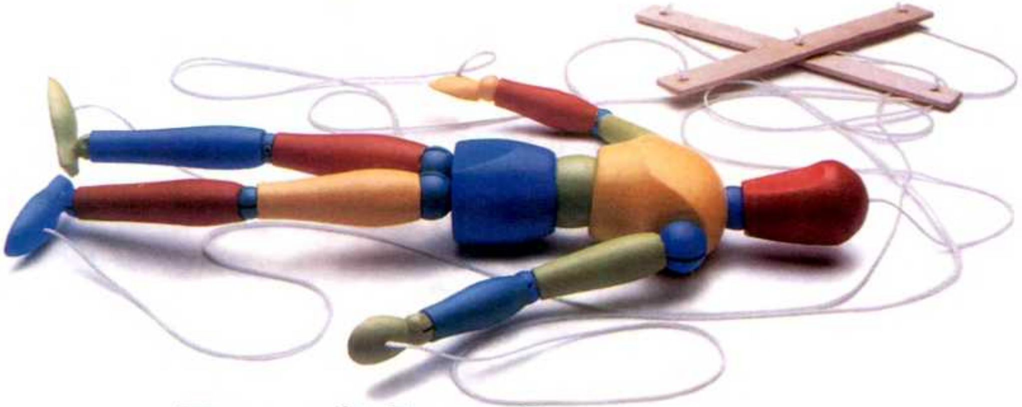

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Abbreviated version of the International summary of product characteristics Therapeutic indications*: Esmeron is indicated as an adjunct to general anesthesia to facilitate tracheal intubation during routine and rapid sequence induction, and to provide skeletal muscle relaxation during surgery. Esmeron is also indicated as an adjunct in the intensive care unit (ICU) to facilitate tracheal intubation and mechanical ventilation. **Contra-indications** Former anaphylactic reactions to rocuronium or to the bromide ion. **Special warnings and special precautions for use** Since Esmeron causes paralysis of the respiratory muscles, ventilatory support is mandatory for patients treated with this drug until adequate spontaneous respiration is restored. As with all neuromuscular blocking agents, it is important to anticipate intubation difficulties, particularly when used as part of a rapid sequence induction technique. Although very rare, severe anaphylactic reactions to neuromuscular blocking agents, including Esmeron, have been reported. These reactions have, in some cases, been fatal. Due to the possible severity of these reactions, one should always assume that they may occur and take the necessary precautions. Dose levels greater than 0.9 mg rocuronium bromide per kg body weight may increase the heart rate; this effect could counteract the bradycardia produced by other anesthetic agents or by vagal stimulation. In general, following long term use of muscle relaxants in the ICU, prolonged paralysis and/or skeletal muscle weakness has been noted. In order to help preclude possible prolongation of neuromuscular block and/or overdosage it is strongly recommended that neuromuscular transmission is monitored throughout the use of muscle relaxants. In addition, patients should receive adequate analgesia and sedation. Furthermore, muscle relaxants should be titrated to effect in the individual patients by or under supervision of experienced clinicians who are familiar with their actions and with appropriate neuromuscular monitoring techniques. Because Esmeron is always used with other agents and because the occurrence of malignant hyperthermia during anesthesia is possible, even in the absence of known triggering agents, clinicians should be familiar with early signs, confirmatory diagnosis and treatment of malignant hyperthermia prior to the start of any anesthesia. In animal studies, Esmeron was shown not to be a triggering factor for malignant hyperthermia. **The following conditions may influence the pharmacokinetics and/or pharmacodynamics of Esmeron:** *Hepatic and/or biliary tract disease and renal failure.* Because rocuronium is excreted in urine (up to approximately 30% within 12-24 hours) and it is expected that it is also partly excreted in bile, Esmeron should be used with caution in patients with clinically significant hepatic and/or biliary diseases and/or renal failure. In these patient groups prolongation of action has been observed with doses of 0.6 mg rocuronium bromide per kg body weight. *Prolonged circulation time.* Conditions associated with prolonged circulation time such as cardiovascular disease, old age and edematous state resulting in an increased volume of distribution, may contribute to a slower onset of action. *Neuromuscular disease.* Like other neuromuscular blocking agents, Esmeron should be used with extreme caution in patients with a neuromuscular disease or after poliomyelitis since the response to neuromuscular blocking agents may be considerably altered in these cases. The magnitude and direction of this alteration may vary widely. In patients with myasthenia gravis or with the myasthenic (Eaton-Lambert) syndrome, small doses of Esmeron may have profound effects and Esmeron should be titrated to the response. *Hypothermia.* In surgery under hypothermic conditions, the neuromuscular blocking effect of Esmeron is increased and the duration prolonged. *Obesity.* Like other neuromuscular blocking agents, Esmeron may exhibit a prolonged duration and a prolonged spontaneous recovery in obese patients, when the administered doses are calculated on actual body weight. *Burns.* Patients with burns are known to develop resistance to non-depolarizing neuromuscular blocking agents. It is recommended that the dose is titrated to response. **Conditions which may increase the effects of Esmeron** Hypokalemia (e.g. after severe vomiting, diarrhea and diuretic therapy), hypermagnesemia, hypocalcemia (after massive transfusions), hypoproteinemia, dehydration, acidosis, hypercapnia, cachexia. Severe electrolyte disturbances, altered blood pH or dehydration should therefore be corrected when possible. Therapeutic indications may vary from country to country. *For full prescribing information see your local package insert. December 1999

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Editorial Notices

STRUCTURED ABSTRACTS

From January 2002, the Summary of all Clinical Investigations, Laboratory Investigations and Short Communications (but not Reviews, Case Reports or Commentaries) published in the *British Journal of Anaesthesia* will be structured under the headings:

Background
Methods
Results
Conclusions

All new manuscripts submitted to the *British Journal of Anaesthesia* should therefore be presented in this format. If an Editor asks for a revised version of a previously submitted manuscript, please change the Summary in your next draft to the new structured format.

Jennifer M. Hunter
Editor-in-Chief

$500,000 IARS Frontiers in Anesthesia Research Award—Fourth Recipient

The Board of Trustees of the International Anesthesia Research Society (IARS) announced at the 75th Clinical and Scientific Congress the fourth recipient of the $500,000 IARS Frontiers in Anesthesia Research Award. The award was established by the IARS in 1994 'to foster innovation and creativity by an individual scientist in the field of Anesthesiology'. The fourth recipient is:
Mark A. Schumacher, PhD, MD, University of California, San Francisco, California.

Dr Schumacher's research project is titled 'Stretch-Inactivated Channels in Pain Transduction'. Dr Schumacher is an Assistant Professor in the Department of Anesthesia and Perioperative Care at the School of Medicine, University of California, San Francisco.

3rd National Conference Indian Society of Neuroanaesthesiology and Critical Care (ISNACC-2002)

Mumbai, India, January 12–13, 2002

Venue: Choksi Auditorium, Tata Memorial Hospital, Parel, Mumbai.

For further details contact: Dr (Mrs) Kanchan S. Jagger, Room No. 423, 4th Floor, Department of Anaesthesia, L.T.M. Medical College Sion, Mumbai: 400022, India. Tel: +91 22 4022976 (O), +91 22 4371811 (R); Fax: +91 22 4076100; Email: kanchanjagger@yahoo.co.uk or isnacc2002@sify.com

20th Annual Symposium Clinical Update in Anaesthesiology and Advances in Techniques of Cardiopulmonary Bypass

Paradise Island, Bahamas, January 13–19, 2002

Abstract, Poster and Free Papers Information: (**Deadline – November 1, 2001**) Helen Phillips, Mount Sinai Medical Center, 1 Gustave L. Levy Place, Box 1010, New York, NY 10029-6574, USA. Tel: +1 212 241 7467; Fax: +1 212 426 2009; E-mail: helen.phillips@mssm.edu

Welcome to the second Euro-PNB winter symposium!

Postgraduate Course on Peripheral Nerve Blockade in Surgery and Pain Management for anaesthesiologists Excelsior Mila Hotel, Crans-Montana, Switzerland, January 16–19, 2002

Meet European experts in this stimulating course with workshops in an exciting environment.

Lecturers: Borgeat, Zürich, CH; J. Büttner, Mumau, DE; X. Capdevila, Montpellier, FRA; A. Ekblom, Stockholm, SE; E. Gaertner, Strasbourg, FRA; S. Gligorijevic, Zürich, CH; M. Jöhr, Luzern, CH; Z. Kosciclniak-Nielsen, Copenhagen, DK; D. Selander, Södertälje, SE; N. Suthcliffe, Glasgow, UK; T. Wildsmith, Dundee, UK.

Full participation certifies 15 Eu CME points. Fee: 250.-CHF. Places are limited to 40 delegates.

Registration before December 1, 2001 to: Assoc. Prof. Alain Borgeat, Head of Anaesthesia and Intensive Care, Orthopedic University Clinic, Balgrist/Zürich, Forchstrasse 340, CH-8008 Zürich, Switzerland.
Tel: +41 1 386 38 32; Fax: +41 1 386 16 09; E-mail: aborgeat@balgrist.unizh.ch

13th SW Thames Anaesthesia Update

Belle Plagne, French Alps, January 28–February 1, 2002

The scientific programme will include lectures and discussions on: Acute and Chronic Pain; Paediatric Update; Obstetric Anaesthesia; Neurology and Anaesthesia; ITU and Relevant Medical Topics; Cardiothoracic Anaesthesia; Day Case Surgery; Regional Blocks; New Drugs Update; Training and Education; Information Technology; Free Papers. Case Presentation Competition. Guest Speakers, Workshops, Videos on new Drugs, Equipment and Techniques.

Open to all anaesthetists. Anaesthetists in training presenting papers are eligible for prizes. Deadline for abstracts: December 10, 2001. Meeting approved for CEPD.

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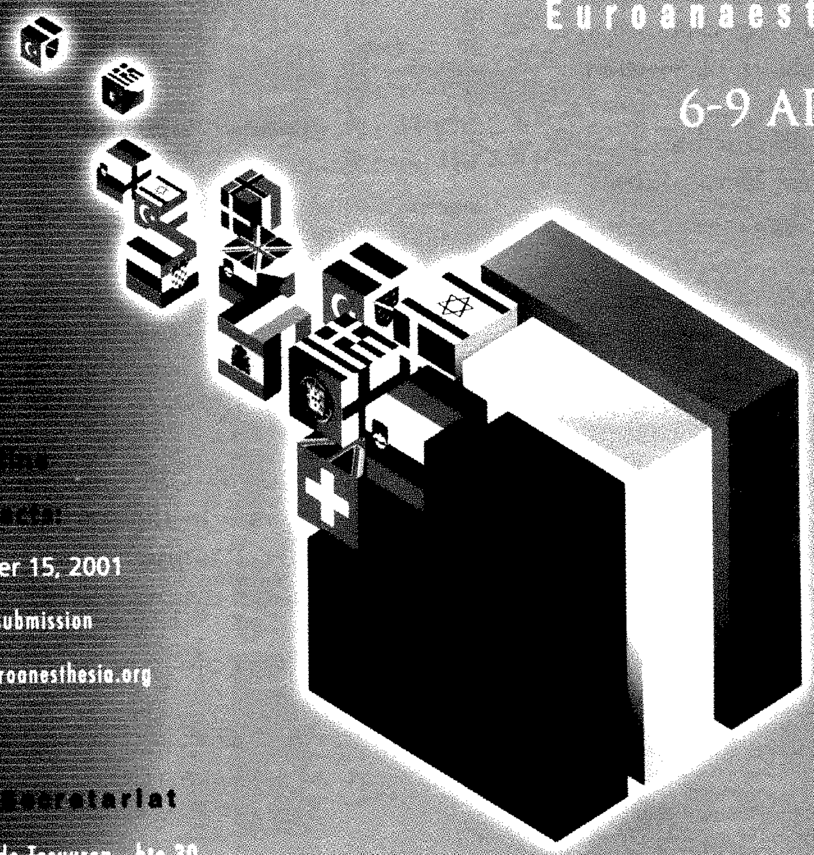

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10th Winter Symposium on Intensive Care Medicine

Crans Montana, Switzerland, February 3–8, 2002

For further details, please contact: Mrs Veronique De Vlaeminck, Department of Intensive Care – Symposium, Erasme University Hospital, Route de Lennik 808, B-1070 Brussels, Belgium. Tel: +32 2 555 47 57; Fax: +32 2 555 45 55; Email: sympicu@ulb.ac.be

The Mersey School, Anaesthesia and Perioperative Medicine and The Section of Anaesthesia, The Royal Society of Medicine For Anaesthetists only: Challenge, Concern, Frustration and Despair—Performance, Risk Management, Appraisal and Revalidation

The Liverpool Maritime Museum, Liverpool, UK, February 6, 2002, 9.30–16.30

For further details, please contact: Dr D. Gray, Potgraduate Medical Centre, Broadgreen Hospital, Liverpool L14 3LB, UK. Tel: +44 (0)151 529 5809

9th Annual Paediatric Anaesthesia Update

The Manchester Conference Centre, Weston Building, Sackville Street, Manchester, UK, February 15, 2002

A repetition of this highly successful CME approved course, with a selection of topical reviews intended for consultant and trainee anaesthetists with an interest in paediatric anaesthesia.

Fee: £150 includes coffee, lunch, tea and course booklet. For further information please contact: The Secretary, University Department of Anaesthesia, Royal Manchester Children's Hospital, Hospital Road, Pendlebury, Manchester, M27 4HA, UK. Tel/Fax: +44 (0)161 727 2291. Email: jonespa@zoom.co.uk

Legal and Ethical Issues in Anaesthesia and Critical Care

Clinical Education Centre, Glenfield Hospital, Leicester, February 22, 2002

For further information please contact: Conference Co-ordinator, Clinical Education Centre, Glenfield Hospital, Groby Road, Leicester LE3 9QP, UK. Tel: +44 (0)116 250 2305; Fax: +44 (0)116 256 3334; Email: jackie.howarth@uhl-tr.nhs.uk

International Anaesthesia Research Society Annual Clinical and Scientific Congresses

March 16–20, 2002

IARS 76th Clinical and Scientific Congress, San Diego Marriott Hotel & Marina, San Diego, California, USA.

March 22–26, 2003

IARS 77th Clinical and Scientific Congress, New Orleans Marriott, New Orleans, Louisiana, USA.

March 27–31, 2004

IARS 78th Clinical and Scientific Congress, Tampa Marriott Waterside Hotel, Tampa, Florida, USA.

March 11–15, 2005

IARS 79th Clinical and Scientific Congress, Hilton Hawaiian Village, Honolulu, Hawaii, USA.

Contact information: IARS, 2 Summit Park Drive, Suite 140, Cleveland, OH 44131, USA. Tel: +1 216 642 1124; Fax: +1 216 642 1127; E-mail: iarshq@iars.org; Web: www.iars.org

22nd International Symposium on Intensive Care and Emergency Medicine

Congress Center, Brussels, Belgium, March 19–22, 2002

For further details, please contact: Mrs Veronique de Vlaeminck, Department of Intensive Care, Erasme University Hospital, Route de Lennik 808, B-1070 Brussels, Belgium. Tel: +32 2 555 32 15/36 31; Fax: +32 2 555 45 55; Email: Veronique.De.Vlaeminck@ulb.ac.be Website: http://www/intensive.org

Putting New Flesh on Old Bones: a major conference on Issues in the Perioperative Care of Geriatric Trauma

The Netherwood Hotel, Grange-Over-Sands, UK, May 10, 2002

Speakers include: Nigel Sharrock (New York); Martyn Parker (Peterborough)

Deadline for free paper abstracts: February 1, 2002.

Please contact Dr Andrew Severn for details: Tel: +44 (0)1524 583517; Fax: +44 (0)1524 583519.

Australian and New Zealand College of Anaesthetists Annual Meeting

Brisbane Convention and Exhibition Centre, Brisbane, Australia, May 11–15, 2002

For further information please contact:

ANZCA 2002 Secretariat, PO Box 1280, Milton QLD 4064, Australia.

Tel: +61 (0) 7 3858 5537; Fax: +61 (0) 7 3858 5510;
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Royal Australasian College of Surgeons and The Royal College of Surgeons of Edinburgh, Annual Scientific Congress

Adelaide, Australia, May 11–15, 2002

A joint meeting of the colleges to celebrate the 75th anniversary of the Australasian College. A team of speakers will address: Clinical Governance, Quality in Surgical Education, Remote and Rural Surgery, Medical Legal Problems, Colorectal Surgery, Paediatric Surgery, and Trauma.

Closing date for abstracts: January 25, 2002. Abstracts should be submitted electronically: http://www.surgeons.org

Registration for Fellows of the Royal College of Surgeons of Edinburgh will be through this College. Please contact: Mrs Maureen Lowrie in the Education Section of the College. Tel: +44 (0)131 668 9209; Fax: +44 (0)131 668 9241. Email: m.lowrie@rcsed.ac.uk

First World Congress on Regional Anaesthesia and Pain Therapy

Barcelona, Spain, June 5–8, 2002

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; Email: dionne@options.com.cy

XVIth Edinburgh Anaesthesia Festival

Edinburgh, UK, August 21–23, 2002

A three-day programme consisting of lectures and discussion on current topics in anaesthesia.

For further details, please contact: University Department of Anaesthesia, Critical Care and Pain Medicine, Royal Infirmary, Lauriston Place, Edinburgh EH3 9YW, UK. Tel: +44 (0)131 536 3652; Fax: +44 (0)131 536 3672. Email: anaes@ed.ac.uk

Anaesthesia outside the square: CECANZ Conference 2002

Christchurch, New Zealand, September 18–20, 2002

For information, please contact: Conference Secretariat Joy Mehlhopt, Conference Innovators, P.O. Box 1370, Christchurch, New Zealand.

Tel: +61 3 379 0390; Fax: +61 3 379 0460; E-mail: joy@conference.co.nz. Website: www.cecanz2002.org.nz

Société Française d'Anesthésie et de Réanimation

Annual congresses will take place in Palais des Congrés, Porte Maillot, Paris on the following dates:

September 26–29, 2002
September 18–21, 2003
September 20–October 3, 2004
September 29–October 2, 2005

For further information, please contact: SFAR, 74, rue Raynouard, F-75016 Paris, France. Tel: +33 1 45 25 82 25; Fax: +33 1 40 50 35 22; E-mail SFAR@invivo.edu

Dingle 2002—4th Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 2–6, 2002

For further information contact: Dr Monty Mythen, Director, Centre for Anaesthesia, UCL, Room 103, 1st Floor Crosspiece, Middlesex Hospital, London, W1T 3AA, London, UK. Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com

Australian Society of Anaesthetists National Scientific Congress

Adelaide, Australia, October 26–30, 2002

This is the Society's premier scientific conference, held in an interesting part of the world.

For further details, please contact: Festival City Conventions, P.O. Box 949, Kent Town, S.A. 5071, Australia. Tel: +61 (0)8 8363 1307; Fax: +61 (0)8 8363 1604: E-mail: asa2002@fccconventions.com.au

8th International Congress of Cardiothoracic and Vascular Anesthesia
19th International Congress of the Israel Society of Anesthesiologists

Jerusalem, Israel, November 10–13, 2002

For further information regarding the Congress, please contact:

8th International Congress of Cardiothoracic and Vascular Anesthesia, PO Box 50006, Tel Aviv 61500, Israel

Tel: +972 3 5140000; Fax: +972 3 5140077; E-mail: anesth2002@kenes.com

Web address: http://www.isranest.org.il/congress 2002

German Congress of Anaesthesiology 2002 (DAK 2002)

Messezentrum Nürnberg, June 26–29, 2002

German Congress of Anaesthesiology 2003 (DAK 2003)

Messezentrum Nürnberg, June 18–21, 2003

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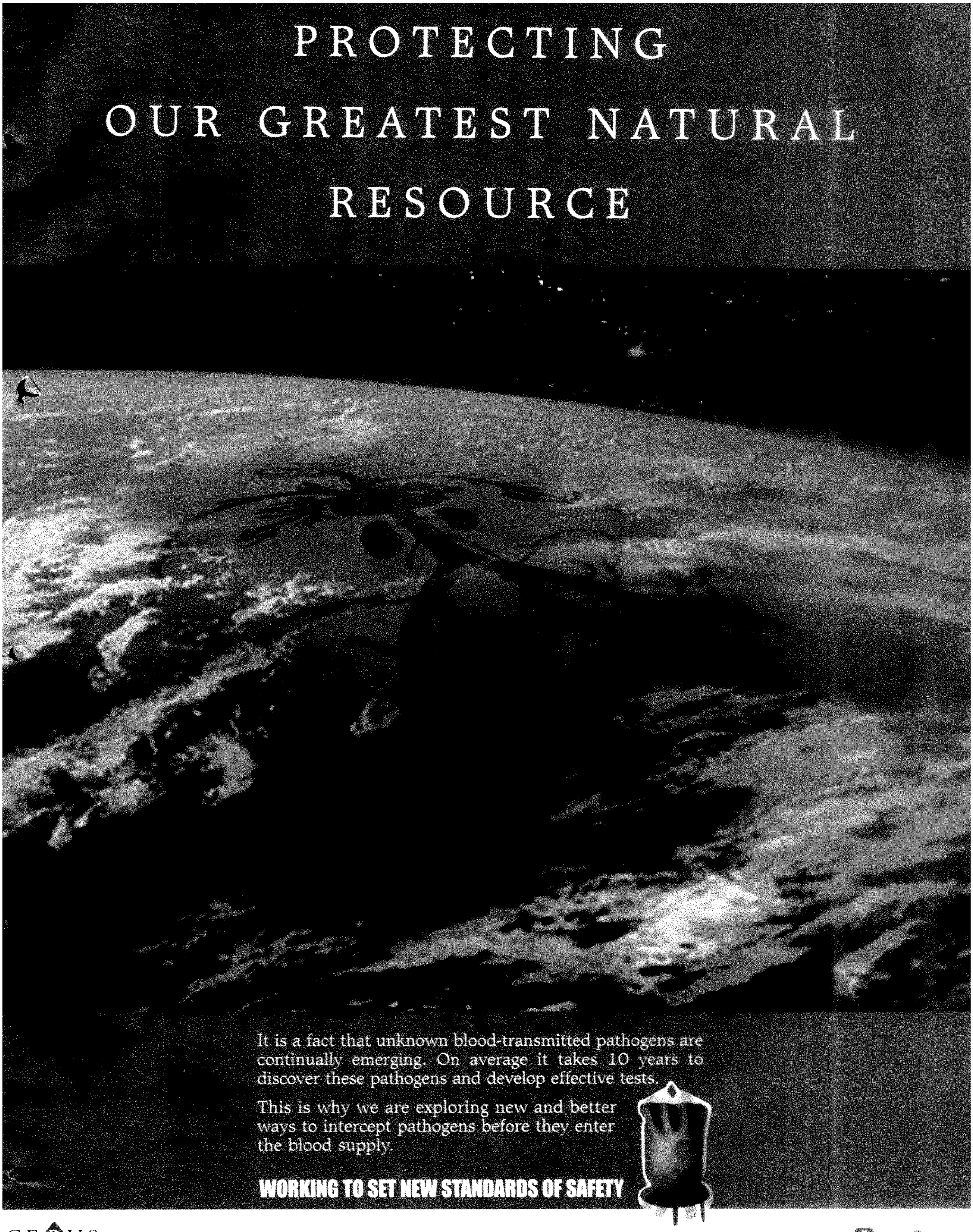

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Helsinki, Finland, August 16–20, 2003

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For further information please contact: Prof. Per H.Rosenberg, Helsinki University Hospital, Helsinki FIN00029 HUS, Finland.

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Dingle 2003—5th Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 1–5, 2003

For further information contact:

Dr Monty Mythen, Director, Centre for Anaesthesia, UCL, Room 103, 1st Floor Crosspiece, Middlesex Hospital, London, W1T 3AA, London, UK. Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com

13th World Congress of Anaesthesiologists

Palais des Congrès de Paris, Paris, France, April 18–23, 2004

For further details, please contact the Congress Office at: COLLOQUIUM, 12 rue de la Croix Faubin, F-75557 Paris cedex 11, France. Tel: +33 (0) 1 44 64 15 15. Fax: +33 (0) 1 44 64 15 16/17. Email: wca2004@colloquium.fr Website: www.wca2004.com

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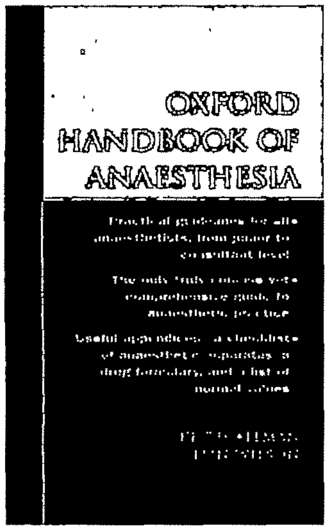

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"I would have everie man write what he knowes and no more."—Montaigne

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Editorial I

The sitting position in neurosurgery—not yet obsolete!

The 1960s and the 1970s were the heyday for the popularity of the sitting position for surgical procedures involving the cervicodorsal spine and the posterior and lateral cranial fossae.[1] This patient position provides optimum access to midline lesions, improves cerebral venous decompression, lowers intracranial pressure (ICP), and promotes gravity drainage of blood and cerebral spinal fluid (CSF).[2] Accumulated blood drains out of and away from the operative site in the sitting position, permitting more rapid access to bleeding points, a cleaner surgical field and a technically easier procedure than is possible in the prone position. In addition, the sitting position provides an unobstructed view of the patient's face, enabling observation of motor responses to cranial nerve stimulation. In some procedures, notably supracerebellar, infratentorial approaches to the pineal gland, the sitting position minimizes the amount of cerebellar retraction needed to gain access to deeper structures. Complications related to the use of this position include haemodynamic instability, venous air embolism (VAE) with the possibility of paradoxical air embolism, pneumocephalus, quadriplegia, and compressive peripheral neuropathy.[3]

Although there have been a number of studies substantiating the relative safety of the sitting position for neurosurgery, its use remains controversial and appears to be diminishing because of the potential for serious complications and malpractice liability claims. Alarming reports of postoperative quadriplegia in young patients,[4 5] and successful malpractice liability claims arising from neurological dysfunction secondary to paradoxical air embolism (PAE) (J. D. Michenfelder, personal communication), has resulted in a dramatic decline in the UK and in the US in the use of the sitting position for neurosurgery. Campkin and colleagues[6] reported that 19 (53%) of the 36 UK neurosurgical centres surveyed in 1981 used the sitting position for posterior fossa surgery and 11 (30%) for cervical spinal surgery. Elton and Howell[7], based on a postal survey of UK neurosurgical centres, claimed a greater than 50% reduction in the number of neurosurgical centres using the sitting position during the decade, 1981–1991. In 1991, patients were normally placed in the sitting position for posterior fossa surgery in eight (20%) of the UK centres surveyed compared with 19 (53%) in 1981. Black and colleagues[8] also reported a major change from sitting to horizontal position for patients undergoing posterior fossa craniotomies over the 4-yr period from 1981–1984 at the Mayo Clinic. Posterior fossa craniotomies performed in the sitting position in that institution declined from over 110 per yr in the early 1980s to less than 50 by the mid decade. Responses to a recent questionnaire issued to 61 Japanese neurosurgical institutions reflects a similar decline with only 11.5% of centres reporting continued use of the sitting position.[9] As neurosurgeons abandon its application, it is likely that this trend will continue, as trainees in neurosurgery are not exposed to the relative merits of sitting position surgery.

Will specific difficult surgical access cases be denied the technical advantages of the sitting position in the future? Is the increasing preference for use of horizontal positions for surgical access to the posterior fossa appropriate, or should limited use of the sitting position remain in the neurosurgeon's armamentarium? Large prospective randomized controlled trials examining outcomes following neurosurgical procedures performed in the sitting compared with the prone or lateral positions are now unlikely to be undertaken. Current best available evidence is largely derived from data published following retrospective observational studies.

Harrison and colleagues report their experience of the use of the sitting position in 407 paediatric neurosurgical procedures performed over a 16-yr period at the Great Ormond Street Hospital for Children, London in this issue of the Journal.[10] This large retrospective observational study focuses on the incidence of VAE in this paediatric population, and on the important clinical issue of subsequent patient outcome. The authors report a low incidence of both VAE (9.3%) and associated postoperative morbidity, and they advocate the continued use of the sitting position in selected paediatric neurosurgical cases. The impressively low incidence of capnography-detected VAE in this Great Ormond Street paediatric series was remarkable considering the institution's minimalist intervention policy in terms of preoperative contrast echocardiography, central vein cannulation and use of anti-gravity suits However, retrospective studies, such as this, rely on the accuracy of clinical detection and recording, and they may underestimate the true incidence of VAE. Despite such

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limitations, this observational study provides a significant body of data on the incidence and outcome of VAE in children. Duke and colleagues recently retrospectively reviewed morbidity related to intraoperative VAE in the sitting compared with supine position in 432 consecutive adult neurosurgical procedures performed at the Mayo Clinic.[11] Although the incidence of VAE detection in seated patients was higher (28 *vs* 5%), there was no significant difference in morbidity related to VAE.

Assessment of the relative risk-benefit of sitting position surgery for the individual patient, based on physical status and specific intracranial pathology is, therefore, of paramount importance. Appropriate patient selection, anticipation of potential complications and careful perioperative monitoring facilitate safe use of the sitting position. Preoperative contrast echocardiography is frequently performed for identification of patients at risk of PAE due to the presence of a patent foramen ovale (PFO). Weihs and colleagues[12] detected a PFO in 28% of a series of 165 adult neurosurgical patients using preoperative contrast echocardiography, which concurs with the findings of a large autopsy series which found an incidence of asymptomatic probe-patent PFO of 27%.[13] Using preoperative Doppler colour-flow imaging, in 30 children undergoing sitting position surgery, Fuchs and colleagues reported a PFO detection rate of 20%.[14] Although transoesophageal echocardiography (TOE) is currently the most sensitive monitoring device, its sensitivity in detecting PFO is not absolute,[15] and PAE has occurred despite absence of an interatrial connection on preoperative testing.[16]

The preoperative identification of a PFO has significant implications for subsequent patient management. We and others consider the preoperative presence of a PFO to be an absolute contraindication to sitting position surgery in view of the risk of PAE.[1 17] In contrast, Duke and colleagues using TOE imaging detected a PFO intraoperatively in 14% of 126 sitting position patients, and report that although the surgical position was not changed, PAE was not detected in any patient.[11] Practices vary regarding the routine preoperative screening of children for PFO prior to sitting position surgery. Preoperative screening was not performed in the series reported by Harrison's group[10] and although the authors advocate the safety of the sitting position in children based on their experience, extreme caution is advised in considering use of this surgical position in children potentially at risk of PAE.

The reported incidence of VAE associated with sitting neurosurgical procedures varies considerably, ranging from 25%[18] to 76%[17] depending on the sensitivity of the monitoring modality used. Monitoring techniques include capnography, precordial Doppler, TOE, fractional excretion of nitrogen, oesophageal stethoscope, and transcutaneous oxygen measurement.[1] Transoesophageal echocardiography is the most sensitive monitor to detect air in the right atrium and paradoxical embolisation to the left atrium through a PFO.[19] A prospective study to determine the clinical significance of small numbers of intracardiac microbubbles detected by TOE may be difficult. Mammotto and colleagues[20] prospectively graded the severity of TOE-detected VAE using a microbubble score (grade 0–3) in 21 patients undergoing sitting position surgery. VAE was detected in all patients. However PAE occurred only after the most severe grades of VAE (grades 2–3).

The oesophageal stethoscope has traditionally been used for diagnosis of VAE. However detection of a 'mill-wheel' murmur is dependant on large volumes of intracardiac air and, therefore, provides little advance warning of impending cardiovascular collapse. Precordial Doppler ultrasonography is the most sensitive of the generally available monitors capable of detecting intracardiac air.[20 21] The pulmonary artery catheter has been evaluated as a diagnostic tool for VAE detection.[22] An increase in pulmonary artery pressure provided a semi-quantitative estimate of the volume of intravascular air. The progressive decrease in lung perfusion caused by air within the pulmonary circulation leads to increased physiological deadspace, which is reflected by a decrease in end-tidal carbon dioxide concentration ($\mathrm{E}'_{\mathrm{CO}_2}$), and an increase in end-tidal nitrogen. Continuous $\mathrm{E}'_{\mathrm{CO}_2}$ monitoring offers intermediate sensitivity with respect to VAE detection.[1] In the series reported by Harrison and colleagues,[10] capnography was used routinely for detection of VAE, with every fall from baseline $\mathrm{E}'_{\mathrm{CO}_2}$ of $\geqslant 0.5$ kPa recorded as an episode of VAE, whether or not there was any associated cardiovascular instability. The use of capnography, a less sensitive monitoring modality for VAE detection, is likely to have contributed to the finding of a lower incidence of VAE (9.3%) in this series than has been previously reported in adult,[17 20] and paediatric studies[14] using Doppler and/or TOE monitoring.

As no single monitor is completely reliable, use of more than one monitoring modality for VAE detection during sitting position surgery is recommended. Black and Cucchiari[2] recommend a minimum of three monitoring techniques. Placement of a multi-orificed central venous catheter is strongly recommended as a means of aspirating air from the circulation should embolism occur.[22] The junction of the superior vena cava and right atrium is the optimal catheter tip position for maximal efficacy in aspirating air.[23] A number of catheter localization techniques have been described, with the electrocardiographic guided technique[24] and TOE guided placement[25 26] allowing precise catheter positioning.

Harrison and colleagues large paediatric series in this journal issue focused on the important clinical issue of patient outcome following VAE. Associated hypotension occurred in only 2% of the 407 procedures, and the authors reported no perioperative morbidity related to VAE, apart from mild hemiparesis in two patients. Black and colleagues[8] retrospectively reviewed 579 posterior fossa craniectomies performed in either the sitting (n=333) or horizontal position (n=246). VAE occurred significantly more often in the sitting position (45 *vs* 12%). However, no morbidity or mortality was attributed to air embolism. Similarly Matjasko and colleagues,[27] in a review of 554 patients, reported a low overall morbidity (1%) related to the sitting position, with 0.5% attributed to VAE. Duke and colleagues[11] reported a 28% incidence of VAE in the sitting position in a retrospective comparison with the supine position in 432 consecutive schwannoma resections. Postoperative VAE-related morbidity occurred in only one of 222 sitting patients (0.5%).

The low reported morbidity due to VAE in reported retrospective studies might lead to the conclusion that, although venous air emboli occur, they frequently have no serious consequences. However, equally it may be argued that the close vigilance exercised, and sensitive monitoring devices used during sitting position surgery result in early diagnosis and prompt treatment of VAE thus limiting the clinical sequelae. A prudent approach to minimizing the occurrence and consequences of VAE in seated patients should include appropriate patient selection based on individual risk-benefit analysis, preoperative screening to identify the population at risk of PAE, supplementary monitoring to promptly detect and treat VAE, and meticulous surgical technique to reduce venous air entrainment. This approach will allow selected patients to continue to benefit from the optimum surgical access and technical advantages of sitting position surgery.

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Editorial II

Oxygen and elective Caesarean section

It was during the 1960s that it became accepted that additional oxygen was required to maintain adequate saturation during general anaesthesia. If there was a seminal contribution to this process it was the publication of Nunn's serial researches into respiratory function.[1] There has never been a similar defining moment for regional anaesthesia, which can also impair respiratory performance. High blocks that involve paralysis of the intercostal muscles will reduce the contribution of the rib cage to breathing. Satisfactory regional block for Caesarean section requires that Aβ fibres are blocked to the level of the T5 dermatome,[2] and as a consequence there are reductions in maternal peak expiratory flow rate, forced vital capacity, and forced expiratory volume. Despite these changes, maternal oxygen saturation is maintained.[3] Although breathing oxygen enriched air increases maternal oxygen saturation, a maternal rationale for supplementary oxygen has failed to become established. In the 1984 edition of his textbook, Crawford wrote 'it is advisable to provide the mother with supplemental oxygen, via a loosely fitting face-piece, until the time of delivery'. His opinion, widely disseminated through his writings, helped establish the practice of oxygen therapy at Caesarean section, but solely for fetal reasons.[4]

Increasing the inspired maternal oxygen fraction increases oxygen delivery to the fetus. The relationship between maternal and umbilical vein Pa_{O_2} during general anaesthesia for Caesarean section was shown by Marx and colleagues in 1971.[5] Their study demonstrated improvements in time to sustained respiration, and Apgar scores, that would not have been so impressive if they had not included hypoxic and normoxic women with those receiving increasingly hyperoxic mixtures.[5] Improvements in neonatal outcome were not maintained with increasing hyperoxia, but despite this a firm link was established between oxygen therapy and neonatal welfare before the obstetric regional anaesthesia revolution occurred. Ramanathan and colleagues[6] broadly repeated, in essence, the study of Marx and colleagues, but on women receiving epidural anaesthesia. They included a normoxic group, but no women were hypoxic. There was a correlation between maternal and umbilical arterial oxygen tensions, but Apgar scores and umbilical artery pH did not improve with increasing maternal hyperoxia. There was a small difference in base excess between the normoxic and hyperoxic groups that barely justified the authors' claims that hyperoxia improved neonatal acid–base status.[6] Uncritical readers of this study will find support for the fetal rationale of higher inspired maternal oxygen fractions, but the difference reported failed to achieve clinical significance. Following uncomplicated vaginal delivery, umbilical artery pH is below 7.3, and base deficit will be between −6 and −10 mmol litre^{-1}.[7] Any deterioration in acid–base status that is too small to impinge on this range cannot be considered important. Babies born to mothers who breathe air at elective Caesarean section, do not display an important increase in metabolic acidosis.[8]

When the neonatal impact of oxygenation is formally assessed, there is an assumption that potentially confounding factors do not have a significant role. Prolonged uterine incision to delivery time produces worrying metabolic acidosis,[9] but problem cases can be excluded. Aortocaval compression causes hypotension, which, if severe enough, will also produce worrying metabolic acidosis,[7 10] but careful vasopressor use will not produce acidosis of concern.[11] Umbilical artery pH is a reflection of both respiratory and metabolic acidosis, does not correlate with Apgar scores and is a poor indicator of outcome.[12] Apgar scores are not a specific marker for asphyxia, being reduced by drug effects which tend to be benign and reversible, and are of poor predictive value as far as outcome is concerned. In contrast, standard base excess reflects only the metabolic component of acidosis and correlates with neonatal outcome, values greater than −12 mmol litre^{-1} having an association with moderate to severe newborn encephalopathies.[13] As far as elective surgery is concerned, if cord biochemistry is to act as a surrogate marker for neonatal morbidity, then standard base excess is the variable to follow. However, it should be recognized that maternal hyperoxia is unlikely to achieve changes of the magnitude required to alter outcome during elective surgery.

One aspect of elective spinal anaesthesia that is often overlooked by anaesthetists is that there is a small but persistent incidence of neonatal acidosis associated with this technique. One hundred consecutive elective, normoxic, spinal anaesthetics for Caesarean section, in this maternity unit, yielded a mean (SD) base excess of −2.26 (3.3) mmol litre^{-1}. The mean value represents a highly satisfactory state of affairs, but the size of the standard deviation indicates some variability. In fact, 11 women had values consistent with the range for normal vaginal delivery, but one value was in excess of −12 mmol litre^{-1}. Whereas mean values are often reassuring, any potential benefit of maternal hyperoxia on the incidence of neonatal base excess beyond −6 or −10 mmol litre^{-1} does not appear to have been assessed, perhaps because a large study would be required. When the arrival of pulse oximetry allowed women with unsatisfactory respiratory performance to be identified, the routine provision of supplementary oxygen at uncomplicated deliveries ceased in this hospital. Others

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have taken the view that maternal oxygen does no harm, but might possibly do a little good, and have continued its use on that basis.

One early concern about raising oxygen tension in the umbilical vein relates to the ductus arteriosus, which constricts in response to high local oxygen tensions as part of the transition from the fetal to neonatal circulation. With the passage of time this is clearly a theoretical risk that is now largely ignored. In this issue of the Journal, a further concern is raised. Khaw and colleagues[14] have randomized women undergoing elective Caesarean section under spinal anaesthesia to breathe air or oxygen enriched air. The effects of breathing oxygen were confirmed by maternal and cord blood gas analysis, and markers of free radical activity were measured in cord blood at birth. The results show a clear difference between the groups, with greater free radical activity in the neonates born to mothers breathing oxygen enriched air.[14] An immediate caveat is that increased free radical activity may represent yet another surrogate marker for an unfavourable neonatal outcome. At present, we have no means of linking free radical formation with neonatal outcome following elective Caesarean section. The authors point out that in a low risk situation such as elective Caesarean section, a favourable outcome is unlikely to be influenced by maternal hyperoxia. The significance of this finding relates to the use of higher inspired maternal oxygen fractions for the delivery of compromised and premature infants. Indeed, it is possible that as far as hyperoxia is concerned, it might be inappropriate to group compromised term and premature babies together, as prematurity and potential asphyxia may be different risks. The authors note the involvement of hyperoxia in a host of neonatal disorders, from retinopathy to intracranial haemorrhage. One of the studies they list reports an improved outcome in neonates resuscitated with air, as opposed to oxygen, that is attributed to less free radical activity. This finding has changed practice, and this year a neonatal resuscitation manual has ceased to recommend the use of oxygen.[15]

Will this study change anaesthetic practice? One thing that will change is the ability to justify maternal oxygen therapy at elective Caesarean section on the basis that it might do some good, but will not do any harm. The latter position is much weakened by this study, and some will revert to air breathing for elective cases. Giving higher inspired oxygen fractions to mothers whose babies are distressed is a deep-seated reflex. Where gas exchange across the placental unit is threatened, the provision of a steeper gradient may improve exchange without necessarily achieving hyperoxia in the umbilical vein. As the anaesthetist can only speculate on what might be occurring, this is a theoretical point. Maternal oxygen might do some good, and might do a little harm, but which, we can only guess. Whereas some may hesitate, a widespread change in practice in the management of the fetus at risk, resulting from this study alone, is not expected.

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Editorial III

Blood transfusion in critical illness

Transfusing blood to treat anaemia in normovolaemic, critically ill patients, is common practice. It has been estimated that one-third of all patients admitted to intensive care units in the developed world receive blood transfusions.[1] Most intensivists prescribe blood with the belief that it enhances oxygen transport and may, therefore, relieve covert tissue hypoxia. Increasing an anaemic, critically ill patient's plasma haemoglobin concentration by transfusion undoubtedly increases global oxygen delivery but there is no guarantee that an increase in regional oxygen delivery will follow. It is even less certain if increased oxygen delivery after transfusion can promote increased oxygen consumption to relieve tissue hypoxia (pathological supply dependency).

Investigators have tried to establish the existence of pathological supply dependency and define optimal oxygen transport goals in both critically ill and perioperative patients.[2 3] However, they manipulated oxygen transport using fluid, inotropic and vasoactive treatments rather than blood transfusion. A transfusion threshold of 10 g dl^{-1} was standard in these studies. Furthermore, a systematic review suggested that although some perioperative patients may benefit from augmented oxygen delivery, there was little evidence to support this approach in critically ill patients.[4] There have been numerous studies evaluating the effects of blood transfusion on oxygen kinetics in a wide variety of critically ill patients.[5–10] However, all of these studies had small patient numbers and only modest total volumes of blood were administered. Although an increase in oxygen delivery following transfusion was a consistent finding, an associated rise in oxygen consumption was observed only occasionally. A decrease in plasma lactate following transfusion was reported in only one of the studies. These results raised many questions, which include the on-going controversy over the very existence of pathological supply dependency, but it can nevertheless be concluded that there is little evidence that blood transfusion relieves tissue hypoxia in critically ill patients.

Many factors influence a clinician's decision to prescribe blood for a normovolaemic, critically ill patient including: how acutely the anaemia developed, the severity of the associated symptoms, age, and comorbidity. Most intensivists use a numeric transfusion trigger, usually a plasma haemoglobin value, as a threshold below which transfusion is indicated.[11] However, this approach has been criticized as physiological variability, in terms of compensatory increases in cardiac output and oxygen extraction in response to anaemia, limits the usefulness of a single laboratory number as a general transfusion guide. This has led other workers to suggest that clinicians should use a physiological trigger, such as an oxygen extraction ratio greater than 50%, in anaemic patients as an indication for blood transfusion.[12] However, this physiological trigger was calculated from studies of non-critically ill animals in which anaemia was induced by controlled euvolaemic haemodilution. Furthermore, impaired oxygen extraction is not uncommonly observed in human critically ill subjects. Even if the oxygen extraction ratio were a reliable indicator of sub-optimal oxygen delivery resulting from anaemia, it would remain difficult to define a number that could be utilized safely as a transfusion trigger in critically ill patients. Such difficulties surrounding physiological triggers have contributed to the widespread adoption of numerical transfusion triggers in clinical practice.

In 1982, Allen and colleagues suggested the 10/30 rule (10 referring to plasma haemoglobin of 10 g dl^{-1} and 30 to the haematocrit) as a clinically useful transfusion trigger.[13] Although the 10/30 rule was derived from perioperative patient studies, the rule was enthusiastically adopted throughout medical practice. It became particularly popular in critical care medicine because: the daily measurement of plasma haemoglobin was a cheap and routine investigation; a haemoglobin of 10 simplified oxygen kinetic calculations; and it was an easy number to remember! Nevertheless, the 10/30 rule as a transfusion trigger in the critically ill has never been supported by a randomized controlled trial.

Despite the 10/30 rule's past popularity in critical care medicine, the increasing costs and decreasing availability of blood products have forced clinicians to reconsider the rule and ask if a transfusion trigger of less than 10 g dl^{-1} could be used safely. Other reasons to reconsider transfusion triggers include the rare but well-recognized risks of transfusion such as infection with human immunodeficiency and infectious hepatitis viruses, and ABO mismatch. There are three other risks of transfusion that are particularly relevant to critically ill patients. First, blood transfusion can cause leucocytosis that may be of uncertain pathological significance but can certainly cause diagnostic confusion.[14] Secondly, microcirculatory risks may also follow transfusion because storage of blood decreases red cell 2,3-diphosphoglycerate concentrations thus impairing the deformability of the cell. Poorly deformable red cells flow through the microcirculation inefficiently and this may partly explain the poor correlation between blood transfusion and increased oxygen consumption. Marik and colleagues demonstrated increased splanchnic ischaemia following transfusion with old blood in patients with sepsis.[8] Furthermore, in a rat sepsis model, transfusion with fresh blood increased oxygen consumption whereas old blood failed to do so.[15] In summary, blood transfusion

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(particularly with old blood) can paradoxically decrease microcirculatory oxygen delivery and contribute to tissue hypoxia.

Thirdly, *in vitro* studies have suggested that blood transfusion causes immunosuppression by decreasing cell-mediated immunity, reducing non-killer cell activity, suppressing macrophage antigen presentation, altering T-cell ratios, and decreasing the concentrations of cytokines (TNF, IFN-γ, and GM-CSF) that are vitally important in immune responses.[16] Randomized controlled trials studying the effects of allogeneic transfusion in colorectal surgery, demonstrated a correlation between volume of transfusion and the incidence of postoperative infections.[17 18] Although these were perioperative patient studies, they nevertheless suggest that transfusion-associated immunosuppression may occur in critically ill patients. There is evidence that the white cells present in transfused blood are the cause of this immunosuppression.[16] In another study of colorectal surgery patients, there was a lower incidence of post-operative infections in patients transfused with leucocyte-depleted blood.[19] Although leucocyte depletion is a costly process, it has been widely adopted throughout Europe.

In contrast to the abundance of evidence that allogeneic blood transfusion may be detrimental, there is a paucity of literature addressing how well critically ill patients tolerate anaemia. It has been documented that healthy animals and surgical patients cope well with profound anaemia.[20] Other authors have suggested that perioperative bleeding is a more important factor than plasma haemoglobin concentrations in determining postoperative mortality and morbidity. In a surgical study, plasma haemoglobin values as low as 6 g dl^{-1} were well tolerated provided operative blood loss was less than 500 ml.[21] In a large study of Jehovah's Witness patients undergoing major surgery, a 1.4% mortality was attributed to anaemia, with 90% of the deaths occurring in patients undergoing cardiovascular surgery.[22] These studies suggest that plasma haemoglobin measurements significantly less than 10 g dl^{-1} are generally well tolerated by surgical patients. However, it remains unclear if this applies to critically ill patients.

At what plasma haemoglobin concentration do the risks of anaemia outweigh the potential risks of blood transfusion in critically ill patients? When is blood transfusion justified? Until 2 yr ago, there had been only five randomized controlled studies comparing different transfusion strategies in critically ill and perioperative patients.[23–27] Perhaps not surprisingly all of these small studies failed to answer this question. Until recently the only published studies available to help clinicians decide when to transfuse anaemic critically ill patients have been either observational or small, poorly controlled, clinical studies based on peri-operative rather than critically ill patients.

Two years ago, an attempt was made to answer this question when the Transfusion Requirements in Critical Care (TRICC) Investigators, on behalf of the Canadian Critical Care Trials Group, published the results of a large multicentre, randomized, controlled clinical trial of transfusion requirements in critical care.[28] After conducting an observational study to assess transfusion practice variation throughout Canada,[29] the investigators enlisted 838 patients over 3 yr from 25 centres. Only normovolaemic, anaemic (plasma haemoglobin <9 g dl^{-1}) patients who were expected to stay in the intensive therapy unit for more than 24 h were included in the study. Important exclusion criteria were evidence of active bleeding (>3 units transfusion over 24 h), chronic anaemia (plasma haemoglobin <9 g dl^{-1} in the preceding month) and patients undergoing cardiac surgery. The enlisted patients were randomized to receive either a restrictive transfusion strategy (transfusion trigger of 7 g dl^{-1} and a maintenance range of 7–9 g dl^{-1}) or a liberal strategy (transfusion trigger of 10 g dl^{-1} and a maintenance range of 10–12 g dl^{-1}). Single unit transfusions were administered and plasma haemoglobin checked before further transfusion was considered.

The procedures were applied successfully as average daily haemoglobin concentrations were 8.5 and 10.7 g dl^{-1} in the restrictive and liberal strategy groups, respectively. On average, a total of 2.6 units of blood were administered to patients randomized to the restrictive strategy group compared with 5.6 units for patients in the liberal strategy group. Patients in the restrictive strategy group received 54% less blood by volume than patients in the liberal strategy group. One-third of the patients in the restrictive strategy group did not require transfusion whereas all patients in the liberal strategy group were transfused There was a non-significant trend towards decreased 30-day all-cause mortality (the primary outcome measure), in favour of patients in the restrictive strategy group and the same pattern was observed for the secondary outcome measures of 60-day all-cause and ICU mortalities. Also, there was a significantly lower adjusted multiple organ dysfunction score (secondary outcome measure), again in favour of patients in the restrictive strategy group. Subgroup analysis revealed that young patients (<55 yr old), and patients with APACHE II <20 were the only subgroups to have a significantly better primary outcome measure after randomization to the restrictive strategy group. There was no significant difference between the two strategies for any other subgroups including patients with septic shock and with cardiovascular disease. There were significantly fewer cardiac complications, including acute myocardial infarction and pulmonary oedema, observed in patients in the restrictive strategy group

The TRICC investigators concluded that a restrictive strategy is at least comparable with a liberal strategy in critically ill patients and may be better because it is associated with· a trend towards improved 30-day all-cause mortality; a significant decrease in hospital mortality, adjusted multiple organ dysfunction score, and cardiovascular complications; and decreased transfusion by 54% and transfusion exposure by 33%. The TRICC investigators recommended the restrictive strategy as best practice for most patients including those with cardiovascular disease, but with the possible exception of critically ill patients with on-going coronary ischaemia. Doubt about the appropriateness of a restrictive strategy approach for such patients was supported by the publication of a later subgroup analysis that suggested that patients with severe cardiac disease randomized to the restrictive strategy group had a non-significant increase in 30-day all-cause mortality.[30] Unfortunately, the TRICC study excluded patients with chronic anaemia and those undergoing cardiac surgery and so it remains difficult to recommend a transfusion strategy for either of these groups on the basis of this study.

Most studies addressing transfusion practice in critically ill patients have been conducted in North America. However, a prospective, epidemiological survey of anaemia and transfusion practice in Western Europe (Anaemia and Blood Transfusion in Critical Care Study) has been completed but the results await publication. In the long term, new therapies such as human recombinant erythropoietin and artificial blood substitutes may decrease blood transfusion requirements. However, at this moment the simplest, safest, and most cost-effective way to reduce transfusion requirements in critically ill patients is the adoption of a lower transfusion trigger as suggested by the TRICC investigators, rather than the premature introduction of clinically unproven, expensive, new treatments with uncertain safety profiles.

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Editorial IV

Airway management in the emergency department

With the agreement of the Editor-in-Chief of the *British Journal of Anaesthesia* and the editors of the *Emergency Medicine Journal*, this editorial has been published in both journals simultaneously.

In most emergency departments in the UK, tracheal intubation requiring the use of anaesthetic drugs has usually been undertaken by anaesthetists. In contrast, the role of the emergency physician in the management of airway emergencies has been limited to simple airway interventions and intubation of the moribund. There is a general view that a particular clinical procedure (e.g. tracheal intubation) should not be specific to one specialty group, but that whichever specialty group undertakes it the competencies to do so must be the same. The safety of airway management in the resuscitation room will be enhanced greatly by strong cooperation between departments of anaesthesia and emergency medicine.

In the USA and Australia, emergency physicians undertake most of the tracheal intubations in the emergency department. In a recent study from the USA, emergency medicine residents or attending physicians intubated 569 (93%) of 610 patients requiring airway control in the emergency department.[1] Regardless of the specialty of the doctor performing the intubation in the emergency department, it is usually undertaken with the aid of anaesthetic and neuromuscular blocking drugs in the form of rapid sequence *induction*. Emergency physicians in the USA have modified this term and refer to the procedure as rapid sequence *intubation*, which, like rapid sequence *induction*, is often abbreviated to RSI.

In the UK, the specialty of emergency medicine is evolving rapidly. Emergency physicians quite rightly perceive advanced airway management to be a core skill for resuscitating critically ill patients. Many of these doctors have supplemented their minimum anaesthesia/critical care training requirement of 3 months with further training to enable them to undertake rapid sequence induction and tracheal intubation.[2] In two recent surveys, 31%[3] and 56%[4] of rapid sequence inductions in UK emergency departments were undertaken by emergency physicians. The Faculty of Accident and Emergency Medicine recognizes that future emergency physicians should have all the necessary skills to manage the airway for the first 30 min after admission. Inevitably, there will be conflict with some anaesthetists, who perceive themselves as the sole specialists trained appropriately to have this skill.[5] Anaesthetists may question whether emergency physicians should now be trained to perform rapid sequence induction and tracheal intubation How can this training be achieved and how can the skill be maintained?

The dilemma

Many anaesthetists will argue that rapid sequence induction and tracheal intubation should always be undertaken by those most experienced with the technique. This might be particularly true in the emergency department, where circumstances are likely to be challenging. The patients are not fasted; on the contrary, many have full stomachs after consuming food and alcohol for several hours. These patients are often uncooperative and will not be able to provide any relevant medical history Trauma patients may pose specific airway problems, compounded by hypovolaemia and possibly lung injury In the controlled setting of the operating room, the incidence of difficult intubation is 1.15–3.8%;[6] in the emergency department, the incidence is 3.0–5.3%.[7]

Although the debate on airway management in the emergency department has focused on tracheal intubation, induction of anaesthesia in the critically ill patient may present considerably more difficulty and risk than the insertion of a tracheal tube; all intravenous anaesthetics have the potential to produce profound hypotension in hypovolaemic patients. The most important component of this whole intervention is the decision to proceed. Anaesthetists and intensivists may be concerned that they are expected to pick up the longer-term consequences of the emergency physicians' actions, despite having no part in the initial decision to induce anaesthesia and intubate the patient. They may also be concerned that emergency physicians will not have the experience to induce anaesthesia safely in the critically ill patient.

Anaesthetists might argue that they have provided an excellent service to the emergency department in the past. If there is no problem, why fix it? Emergency physicians will counter this by claiming that there is often a significant delay before arrival of the anaesthetist or intensivist in the

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emergency department. In a recent survey of rapid sequence induction and tracheal intubation in the emergency department, it took more than 5 min for the anaesthetist to arrive in 17 out of the 35 cases that were intubated by an anaesthetist.[3] In a survey undertaken in 1995, 31% of the responding emergency medicine consultants claimed that they had experienced difficulty obtaining an anaesthetist.[8] This problem may get worse as, in many hospitals, recruitment of doctors to critical care units is lagging behind the recent increase in the number of critical care beds (personal observation).

In many cases, the anaesthetist responding to a call to the emergency department is relatively inexperienced.[9] Although this person may be perfectly capable of managing the airways of patients in the calm, controlled environment of the operating theatre, they may lack experience in managing critically ill patients in the setting of the emergency department. Not surprisingly, under these circumstances, experienced emergency physicians with a background in anaesthesia may consider themselves better placed to provide timely airway management.

Training of emergency physicians

If emergency physicians in the UK are going to undertake rapid sequence induction of anaesthesia and tracheal intubation, how are they going to be trained and how will they maintain their skills? The acquisition of advanced airway skills will require substantial clinical training and time. The practicalities of developing the training programme have not yet been tackled. This training might usefully be supplemented by a review course, such as the National Emergency Airway Management Course.[10] This 3-day course introduces emergency physicians to rapid sequence induction of anaesthesia and tracheal intubation using a combination of lectures and practical skill stations. The course includes a variety of other techniques for managing the difficult airway. Such a course can serve only as an introduction to the theory of emergency airway management. Simulator training, such as that provided by the Scottish Airway and Ventilation Emergency (SAVE) Course developed in Stirling, Scotland, will be used for both training and skills maintenance.

Emergency physicians are increasingly undertaking additional secondments to departments of anaesthesia/intensive care, typically obtaining substantive 1-yr senior house officer (SHO) posts. Secondments of 3–6 months are unlikely to provide the emergency physician trainee with enough experience in anaesthetizing and managing the airway of critically ill patients. The average 1-yr anaesthetic SHO post will provide plenty of experience in the operating theatre but exposure to critically ill patients may be limited. Emergency physicians are likely to gain more relevant experience in the critical care unit, where they can learn about the initial management of the critically ill patient. During their time in the critical care unit, they could also be involved in the immediate care of critically ill patients in the emergency department. Perhaps the ideal balance in experience would be gained by undertaking a combined period of training in anaesthesia and critical care. These posts would have the additional benefit of increasing collaboration between the critical care unit and the emergency department. Formal rotations could be established between SHO or specialist registrar posts in anaesthesia and emergency medicine.

The maintenance of advanced airway skills may pose a greater problem than their initial acquisition. Emergency physicians working in busy departments may find little difficulty in undertaking intubations frequently. Those in smaller departments will struggle to maintain their skills. Perhaps simulator training supplemented by short secondments to the operating room or critical care unit will provide the required ongoing training. However, once the initial training and maintenance of skills in advanced airway management is achieved, any developing practice of rapid sequence induction of anaesthesia and tracheal intubation by emergency physicians must be audited continuously. This will provide the data to show whether or not emergency physicians have been trained adequately in advanced airway management and will give some indication of the level of activity needed to maintain skills.

Anaesthetists will, of course, continue to have a major role in advanced airway management in the emergency department. We encourage close collaboration between emergency physicians and anaesthetists/critical care physicians, as both have a major contribution to make in managing the critically ill patient. This teamwork will extend to managing the induction of anaesthesia and tracheal intubation in the emergency department.

In collaboration with The Royal College of Anaesthetists (RCA), the Faculty of Accident and Emergency Medicine (FAEM) wishes to develop, implement and evaluate a suitable competency-based training programme for emergency airway management. Representatives from the RCA and FAEM have established the Joint Working Group on Teaching Airway Management to Emergency Practitioners. The whole process may take 5 yr to complete, but it is important that emergency physicians are trained adequately before adopting the skill of rapid sequence induction and tracheal intubation.

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Editorial note

A freely accessible *BJA* archive

From January 2000, the full text of each issue of the *BJA* became accessible electronically to all BJA subscribers through the journal's website (www.bja.oupjournals.org) on a monthly basis. Each subscriber has needed their password to access all issues of the journal published since that date on the world wide web and this arrangement will continue.

The Editorial Board of the *BJA* has now decided, in conjunction with our publishers, Oxford University Press, that this electronic archive will be made freely accessible on the *BJA* website, without the use of a password, once it is over 2 yr old. Thus, from January 2002, the January 2000 will be freely accessible, and in February 2002, the January and February 2000 issues will be available. This rolling programme will allow a slowly increasing archive of this journal to become freely available, with a 2-yr lag time. The Editorial Board is also considering extending this archive to include earlier years; as yet, no decision has been made on this matter.

This development is just one example of the ways in which the Editorial Board is attempting to keep pace with the huge changes occurring in electronic publishing. I welcome readers' constructive comments on this latest development and, indeed, whether they would find it useful to have an extended archive of the *BJA* available electronically.

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BJA

CLINICAL INVESTIGATIONS

The sitting position for neurosurgery in children: a review of 16 years' experience[†]

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Background. Use of the sitting position for neurosurgery is controversial. The main concern is the risk of venous air embolus (VAE) and its sequelae.

Methods. The paediatric neurosurgeons at our institution routinely use the sitting position for posterior fossa and pineal surgery, and a retrospective audit of the incidence of VAE from 1982 to 1998 has been performed.

Results. Venous air embolism, defined as a fall in end-tidal carbon dioxide pressure >0.4 kPa, was detected in 38 of 407 operations (9.3%). A fall in systolic arterial pressure >10% accompanied the VAE in nine out of 43 episodes (20.9%); this represents 2% of all operations. All VAE episodes responded promptly to treatment and there was no perioperative morbidity or mortality directly attributed to it.

Conclusions. This is the largest study of the incidence of VAE in children undergoing neurosurgery. Our results suggest that the sitting position can be used safely for neurosurgery in children.

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Controversy surrounds the use of the sitting position for neurosurgery.[1] The main concern is the risk of venous air embolus (VAE) and its sequelae. The reported incidence of VAE in adults undergoing neurosurgery in the sitting position varies from 7 to 50%.[2–8] Only three studies have looked specifically at the incidence of VAE in children undergoing neurosurgery in the sitting position with a rate of between 26 and 69%. These studies were all relatively small with between 12 and 48 patients studied.[8–10]

The paediatric neurosurgeons at our institution routinely use the sitting position for posterior fossa and pineal surgery, and for selected foramen magnum decompressions (FMD). Following the availability of a capnogram suitable for all paediatric patients, an on-going retrospective audit of the incidence of VAE in the sitting position has been performed. The results provide a much larger body of data than is currently available in the literature on the risk of a clinically significant VAE during neurosurgery in the sitting position in children.

Methods

The case notes of children who underwent neurosurgery in the sitting position between February 1982 and February 1998 were examined retrospectively every 4 yrs. The patients were identified from the neurosurgical database and the operating department records. The case notes were retrieved and the intraoperative position noted; all children who underwent surgery in the sitting position were included in the analysis.

[†] This article is accompanied by Editorial I.

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Physical characteristics, including patient age, weight, and histological diagnosis, were collected. The anaesthesia records were examined for evidence of VAE, defined as a fall in end-tidal $P\mathrm{CO}_2$ greater than 0.4 kPa. Changes in systolic arterial pressure, or heart rate, greater than 10% from baseline, and any association with a fall in end-tidal $P\mathrm{CO}_2$, were recorded. The postoperative notes were studied with reference to the requirement for postoperative positive pressure ventilation and were used together with the follow-up notes to document any unexpected neurological sequelae. The data were entered into a Microsoft Access database for analysis.

More than 90% of the cases were anaesthetized by one of three consultant paediatric neuroanaesthetists (A.M., A.McE., and E.F.). The anaesthetic technique changed with the standard practice for the time. After anaesthetic review, the majority of the children received either oral or i.m. atropine premedication. Induction of general anaesthesia was either inhalation or i.v., dependent on patient preference. Following orotracheal intubation, a balanced maintenance technique with fentanyl, either tubocurarine or vecuronium, and less than 1 MAC concentration of halothane, isoflurane, or sevoflurane delivered in either nitrous oxide/oxygen or air/oxygen mixture was used; air was only available in the last few months of this study. No positive end-expiratory pressure (PEEP) was applied to the lungs and minute ventilation was adjusted to achieve mild hypocapnia.

After induction of anaesthesia, the child was gradually moved to the sitting position over a 5 min period, with arterial pressure monitoring, and given up to 10 ml kg^{-1} of i.v. crystalloid if required. The surgery took place with the child in an operating chair. Children less than 40 kg were positioned with their feet level with their buttocks, while those greater than 40 kg had dependant legs. Monitoring consisted of electrocardiography, capnography, pulse oximetry (from 1986), and direct systemic arterial pressure measurement. The lower alarm limit for the end-tidal $P\mathrm{CO}_2$ value was set 0.5 kPa below the baseline end-tidal value. Venous access was secured with two peripheral i.v. cannulae. Neither central venous lines nor anti-gravity suits were used routinely. Preoperative contrast echocardiography, to screen for a patent foramen ovale, was not routinely performed on children undergoing surgery in the sitting position. Chi-squared analysis was used to determine any difference in the incidence of VAE between patients with different histological diagnosis.

Results

The case notes of 407 children who underwent neurosurgical operations in the sitting position at Great Ormond Street Hospital for Children between February 1982 and February 1998 were studied. Three hundred and seventy-six operations were performed for excision of a posterior fossa mass, 15 for pineal surgery, and 16 for FMD. More than 99% of these operations were performed by one of three paediatric neurosurgeons. The age of the patient ranged from 6 weeks to 17 yrs, with a median age of 5 yr. The median weight was 19 kg, with a range of 3–70 kg. The male to female ratio was 1.5:1. No child had clinical evidence of a septal defect.

Venous air embolism, defined as a fall in end-tidal $P\mathrm{CO}_2$ greater than 0.4 kPa was detected in 38 of 407 patients (9.3%), and occurred more than once during the same procedure in three patients. There were 43 separate episodes of VAE. None of the 11 children who were less than 1 yr old had an episode of VAE. The incidence of VAE was analysed by patient weight and histological diagnosis (Figs 1 and 2). Statistical analysis using the chi-squared test revealed a significantly higher incidence of VAE in patients with pineal tumours compared with those with astrocytoma (P=0.001). There was no significant difference between the incidence of VAE in children undergoing pineal surgery and those with other histological diagnoses. VAE was accompanied by hypotension (>10% fall in systolic arterial pressure) in nine out of 43 episodes (20.9%) (Fig. 3). The three most severe cases of hypotension were as follows.

Case 1: a fall in end-tidal $P\mathrm{CO}_2$ to 1.2 kPa, associated with a 47% reduction in systolic arterial pressure, occurred during sub-occipital craniotomy for resection of a medulloblastoma in a 3-yr-old boy. The response to treatment was prompt. Postoperative examination revealed a mild hemiparesis, which resolved. The hemiparesis was thought not to have been a result of this episode.

Case 2: a fall in systolic arterial pressure of 47%, associated with tachycardia and a fall in end-tidal $P\mathrm{CO}_2$, occurred in a 9-yr-old boy during resection of a meningioma. The estimated intraoperative blood loss was 1900 ml. Postoperative examination revealed mild ataxia and hemiparesis, which subsequently resolved.

Case 3: during a repeat FMD in a 17-yr-old boy, a sudden fall in systolic arterial pressure from 100 to 30 mm Hg, associated with a fall in end-tidal $P\mathrm{CO}_2$ to 2.5 kPa, was recorded. There was an immediate response to i.v. fluids and vasopressors, and a venous bleeding site thought to have been the site for air was found and managed. He made a full postoperative recovery.

The timing of the VAE relative to surgical events was recorded on 27 occasions. Of these, 12 occurred on opening of the dura, four during tumour dissection, and 11 on closure of the dura. There was no unexplained perioperative morbidity or mortality in the patients with VAE that would suggest a paradoxical air embolus. Management of a suspected VAE included immediate bilateral jugular venous compression, covering the surgical field with saline-soaked swabs, and ventilation with 100% oxygen. I.v. fluids were given to increase the venous pressure and maintain arterial pressure.

All children were haemodynamically stable following induction of general anaesthesia and positioning. Intraoperative cardiovascular instability (defined as >10%

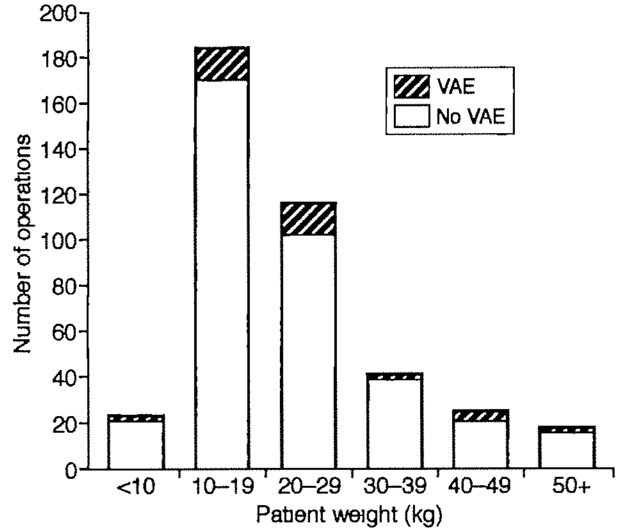

Fig 1 Incidence of VAE during neurosurgery in the sitting position in relation to patient weight.

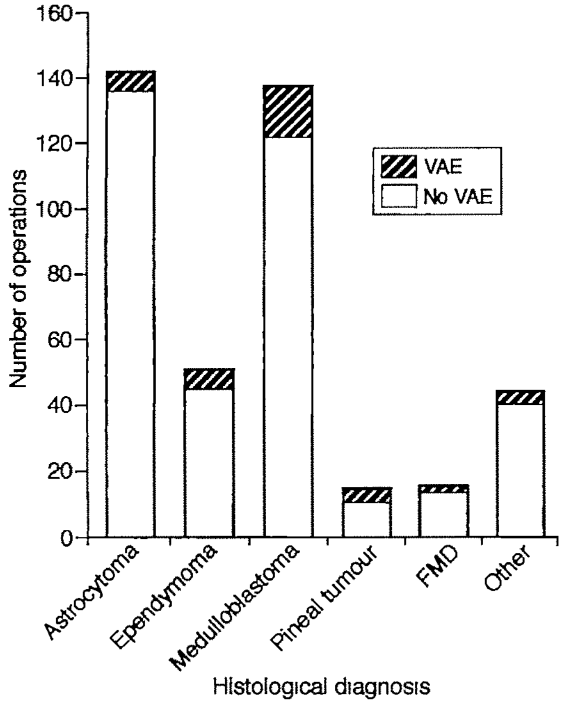

Fig 2 Incidence of VAE during neurosurgery in the sitting position in relation to surgical pathology (FMD = foramen magnum decompressions).

change in systolic arterial pressure, or heart rate, from baseline) occurred in 98 of 407 patients (24.1%). Most were transient bradycardias or tachycardias, with or without hypotension, associated with tumour manipulation. One or more episodes of transient hypotension occurred in 26 patients; they were the result of VAE in eight patients and because of severe blood loss in a further three patients.

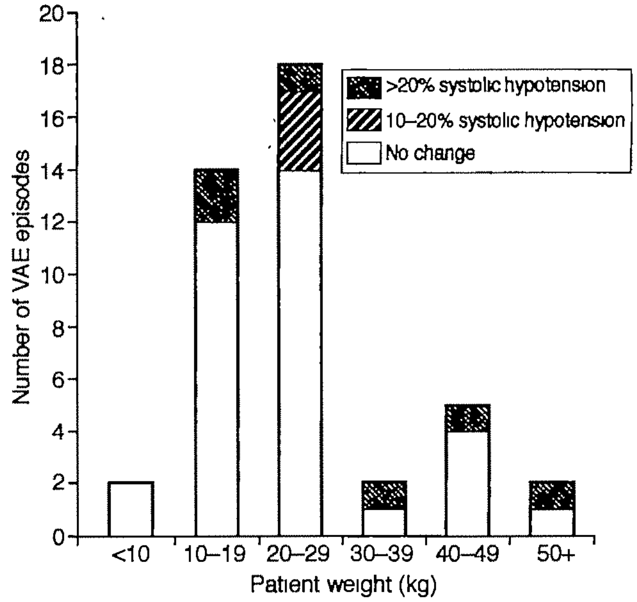

Fig 3 Systolic hypotension associated with VAE.

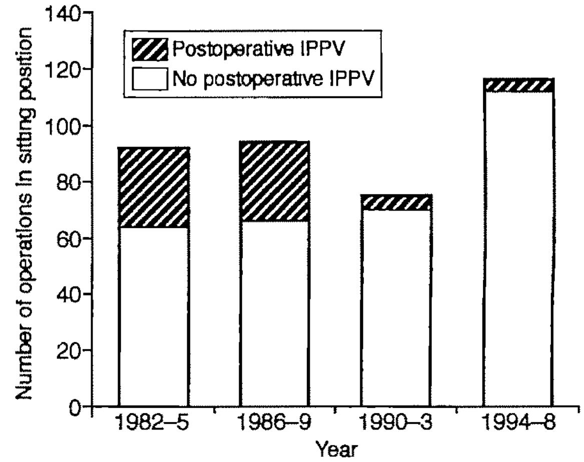

Fig 4 Changes in use of postoperative ventilation with time.

There was no change in the continuously monitored capnograph of the 15 patients in whom the cause for the hypotension was not established.

Sixty-nine of the 407 patients (16.9%) were electively ventilated postoperatively; VAE had occurred in 13 of the 69 cases. Before 1989, patients who were cardiovascularly unstable intraoperatively were electively ventilated, but VAE was not an indication for postoperative ventilation during any part of the study period. Figure 4 shows the change in postoperative ventilation practice with time. Postoperative ventilation was required for more than 72 h in only two patients, neither of whom had evidence of VAE; one because of a bizarre respiratory pattern and the other because of a bulbar palsy. There was no morbidity known to be associated with posterior fossa surgery, such as tension pneumocephalus, macroglossia, quadriplegia, or peripheral nerve damage.

Discussion

The use of the sitting position for neurosurgery is controversial and has been reported to be in decline.[1–12] The main concern is the risk of VAE and its sequelae. Although there are several published reports of the incidence of VAE in the sitting position in adults,[2–7] there are no large series that look at the incidence of VAE in children. The reported incidence, as detected by Doppler ultrasonography, in adults ranges from 7 to 50%.[2–7] We found a lower incidence of VAE in the sitting position in children (9.3%) than previously reported, together with a low incidence of VAE associated hypotension (20.9% of 43 VAE episodes). There are several possible reasons for our findings.

It may be that the incidence of VAE in the sitting position is lower in children than in adults. Although Matjasko and colleagues reported a significantly higher incidence of VAE in children (62%) compared with adults (23%) in a review of 554 neurosurgical procedures in the sitting position, only 13 patients were 12 yrs or less.[2] However, a retrospective comparison between adults and children undergoing sub-occipital craniotomy in the sitting position at the Mayo Clinic showed a lower incidence of VAE in children (16 of 48) than in adult controls (22 of 48).[8] There are two prospective paediatric studies in the literature on the incidence of VAE in the sitting position. Meyer and colleagues reported a 26% incidence of VAE in the sitting position, using capnography, in 30 children who were not treated with lower body positive pressure or PEEP.[9] Fuchs and colleagues studied 24 children undergoing neurosurgery in the sitting position and reported a VAE incidence of 37% as detected by Doppler.[10]

A possible explanation for the low incidence of VAE we report is the finding of relatively high dural sinus pressures in children compared with adults. As a negative venous pressure relative to atmospheric pressure is necessary for venous air entrainment to occur, factors that might affect the intracranial venous pressure in the sitting position have been studied. Iwabuchi and colleagues examined the dural sinus pressure (confluens sinuum pressure, CSP) under various conditions in 47 cases. In the sitting position, all adults had a negative CSP whereas all eight children less than 9 yrs old showed a positive pressure.[12] This difference in CSP in the sitting position between adults and children would suggest a lower risk of VAE in children in this position and may help to explain the low incidence of VAE in our population. However, the findings of Iwabuchi are not supported by those of Grady and colleagues who investigated the relationship of superior sagittal sinus pressure (SSP) to head position in 15 children. In five of the 15 children, the SSP was sub-atmospheric at 90° torso elevation.[13] The effects of PEEP and bilateral internal jugular venous compression, two commonly used treatments for VAE, were also studied. Bilateral jugular venous compression, but not a PEEP of 10 cm H_2O, caused a significant increase in SSP at every degree of head elevation studied.[13] This latter finding supports the value of one of our immediate treatment strategies for a suspected VAE.

It is not possible to directly compare the incidence of VAE between studies where different methods of detection are used. Transoesophageal echocardiography (TOE) is an extremely sensitive method for detecting intracardiac air and it is not surprising that the reported incidence of VAE is as high as 76% in adult studies when TOE is used to detect it.[14] However, TOE will detect tiny microbubbles that may be of no clinical importance. The majority of British practice relies on capnography to detect entrained air that enters the pulmonary circulation. A fall in end-tidal $P\text{CO}_2$ occurs with VAE because air within the pulmonary circulation leads to an increase in physiological deadspace. Capnography is the technique of choice for the detection of VAE at our hospital and has been used for all patients undergoing surgery in the sitting position since February 1982.

We recorded every fall in end-tidal $P\text{CO}_2$ 0.5 kPa as VAE whether or not there was any associated cardiovascular instability. The findings of Mammoto and colleagues support capnography as a satisfactory method for the detection of VAE in the clinical situation.[14] In this study, 21 patients undergoing neurosurgery in the sitting position were continuously monitored with TOE and capnography. Microbubbles appeared in the right atrium in all patients and the severity was graded according to a microbubble scoring system as follows: grade 0 (no microbubbles), grade 1 (less than five microbubbles per frame), grade 2 (10–12 microbubbles per frame), and grade 3 (too many microbubbles to be counted per frame). A fall in end-tidal $P\text{CO}_2$ greater than 0.5 kPa occurred with every episode of grade 2 and grade 3 air embolus.[14]

Cardiovascular instability in addition to a fall in end-tidal $P\text{CO}_2$ implies a larger air embolus than that detected by capnography alone. There is a theoretical argument that the incidence of VAE associated hypotension in children might be higher than in adults. This is because an equivalent air bubble would be larger relative to blood volume in children and, therefore, more likely to cause cardiovascular compromise. This theory is supported by the findings of a comparison between adults and children by Cucchiara and Bowers at the Mayo Clinic.[8] In their retrospective review of 96 patients undergoing sub-occipital craniotomy in the sitting position the incidence of VAE associated hypotension, defined as a fall in systolic arterial pressure of 25 mm Hg, was greater in children (69%) than in adults (36%). However, the two prospective paediatric studies in the literature report conflicting results. Severe hypotension, defined as a fall in mean arterial pressure of at least 25 mm Hg, occurred in all children with VAE, as detected by capnography, in the study by Meyer and colleagues.[9] However, no child developed VAE associated hypotension in the study of 24 children undergoing neurosurgery in the sitting position by Fuchs and colleagues.[10] In our much larger paediatric series we report a low incidence of VAE associated hypotension (nine of 43 VAE episodes or 20.9%). It is not possible to directly compare our results with the incidence of VAE associated hypotension reported in other studies because the definitions used either for the diagnosis of VAE, or hypotension, or both, are different. However, the criteria for hypotension in our study are very strict; had we used Doppler for detection of VAE it is likely that we would have reported a higher number of VAE and consequently an even smaller percentage of VAE episodes with associated hypotension.

There was no clinical evidence of septal defects in our patients but this does not exclude a probe patent foramen ovale which are common in the general population. We do not think, based on our data, that this provides a sufficient risk to warrant routine preoperative echocardiography, while we are aware that any large air embolus may be associated with paradoxical embolism. The routine use of central venous catheters is sometimes recommended.[1] They were not used routinely in our series except to provide good venous access. The most reliable route to the right atrium in small children is via the right internal jugular vein. The flexed head position with the short neck of the child may cause venous obstruction thereby negating the benefits of the sitting position.

In our series apart from two cases of mild hemiparesis, there was no postoperative morbidity in the 38 children in whom a VAE was diagnosed. This lack of associated morbidity following VAE in the sitting position has been confirmed by other large studies.[2,4,5] Reports of complications directly related to the occurrence of VAE are for the most part individual case reports.[16,17] Experience from the Mayo Clinic of 3827 neurosurgical procedures in the sitting position, between 1966 and 1983, revealed only two patients with morbidity related to air embolus; one patient died postoperatively from acute respiratory distress syndrome and the other had a paradoxical air embolus with severe neurological sequelae. The only intraoperative death directly caused by VAE was a patient having surgery in the prone position.[18]

The reasons the sitting position is chosen for posterior fossa surgery in preference to one of the horizontal positions include improved surgical access and orientation, and reduced bleeding. In a retrospective review of 579 posterior fossa craniectomies, Black and colleagues found that the incidence of transfusion of greater than two units of blood was significantly higher in the horizontal than in the sitting patients. Also, postoperative cranial nerve function was significantly better in patients operated on in the sitting position compared to a horizontal position.[1]

The use of a horizontal position does not eliminate the risk of VAE. In a retrospective review of 704 patients undergoing neurosurgery in the lounging position, VAE was detected by Doppler ultrasonography in nine of 34 children (26.5%).[19] Black and colleagues report a 12% incidence of VAE in the horizontal position in 74 adult patients monitored with praecordial doppler.[1] VAE was diagnosed by TOE in eight of 12 infants undergoing craniectomy for repair of craniosynostosis in the supine position in a prospective study by Harris and colleagues.[19]

Although we acknowledge the limitations inherent in a retrospective review, this series provides a much larger body of data on the incidence of VAE in children than is currently available in the literature. Anecdotal evidence and the results of several retrospective adult studies have caused many to abandon the sitting position. We report a low incidence of VAE (9.3%), and VAE associated hypotension occurred in only 2% of 407 operations. Apart from mild hemiparesis, which subsequently resolved, there was no perioperative morbidity or mortality related to VAE over the 16-yr study period. We do not suggest that there should be any complacency about the use of the sitting position but believe that, with meticulous surgical and anaesthetic technique, the position is safe.

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Effects of high inspired oxygen fraction during elective Caesarean section under spinal anaesthesia on maternal and fetal oxygenation and lipid peroxidation[†]

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Background. Oxygen supplementation is given routinely to parturients undergoing Caesarean section under regional anaesthesia. While the aim is to improve fetal oxygenation, inspiring a high oxygen fraction (F_{IO_2}) can also increase free radical activity and lipid peroxidation in both the mother and baby. In this prospective, randomized, double-blind study, we investigated the effect of high inspired oxygen fraction (F_{IO_2}) on maternal and fetal oxygenation and oxygen free radical activity in parturients having Caesarean section under spinal anaesthesia.

Methods. Forty-four healthy parturients were randomized to breathe either 21% (air group) or 60% oxygen (oxygen group) intraoperatively via a ventimask. Maternal arterial blood was collected at 5-min intervals from baseline until delivery, and umbilical arterial and venous blood was collected at delivery. We measured blood gases and the products of lipid peroxidation (8-isoprostane, malondialdehyde (MDA), hydroperoxide (OHP)) and purine metabolites.

Results. At delivery, the oxygen group had greater maternal arterial P_{O_2} [mean 30.0 (SD 6.3) *vs* 14.2 (1.9) kPa; mean difference 15.8 kPa, 95% confidence interval 12.9–18.7 kPa, $P<0.001$] and greater umbilical venous P_{O_2} [4.8 (1.0) *vs* 4.0 (1.4) kPa; mean difference 0.8 kPa, 95% confidence interval 0.0–1.5 kPa, $P=0.04$] compared with the air group. Maternal and umbilical plasma concentrations of lipid peroxides (8-isoprostane, MDA, OHP) were greater in the oxygen group than in the air group ($P<0.05$).

Conclusions. We conclude that breathing high F_{IO_2} modestly increased fetal oxygenation but caused a concomitant increase in oxygen free radical activity in both mother and fetus.

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During spinal anaesthesia, changes in respiratory function occur[1] and oxygen supplementation is commonly given to prevent maternal oxyhaemoglobin desaturation and to optimize fetal oxygenation. Some studies have shown improvement in the umbilical blood gas and acid–base parameters under general and epidural anaesthesia.[2–5] However, Kelly and colleagues showed that administration of 35% oxygen during spinal anaesthesia did not improve fetal umbilical vein P_{O_2} or pH.[1] Few data are available on the efficacy of administering a greater inspired oxygen fraction (F_{IO_2}). Moreover, high F_{IO_2} induces maternal hyperoxia and this may promote the formation of free radicals and lipid peroxidation.

In this randomized, double-blinded study, we investigated the effect of administration of a high F_{IO_2} on maternal and neonatal oxygenation and free radical formation in women having Caesarean section under spinal anaesthesia. The main outcomes we assessed were maternal arterial and

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[†] This article is accompanied by Editorial II.

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Table 1 Indications for elective Caesarean delivery

Indication	Oxygen group (n=22)	Air group (n=22)
Cephalopelvic disproportion or previous Caesarean section	13	13
Breech presentation	6	4
Transverse or unstable lie	0	2
Low-lying placenta or antepartum haemorrhage	2	1
Uterine fibroid	1	1
Genital herpes	0	1

umbilical cord blood gases and maternal and neonatal plasma concentrations of markers of oxygen free radical activity.

Materials and methods

This study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. We recruited 44 ASA I–II non-labouring, term parturients scheduled for elective Caesarean section under spinal anaesthesia after informed written consent. Patients were premedicated with ranitidine 150 mg orally the night before and on the morning of surgery. On arrival at the operating theatre, i.v. access was secured, standard monitoring was attached and a radial arterial cannula was inserted in the non-dominant forearm under local anaesthesia. Patients were then randomized, by drawing shuffled coded opaque envelopes, to breathe either 21% (air group) or 60% oxygen (oxygen group) intraoperatively. Air or oxygen was supplied from the anaesthetic machine (Narkomed 4; North American Dräger, Telford, PA, USA) to a high-flow venturi-type facemask (Intersurgical, Wokingham, UK) to provide the assigned $F\text{I}_{O_2}$. The oxygen analyser of the anaesthesia machine was used to confirm the $F\text{I}_{O_2}$ from the facemask before each use.

Spinal anaesthesia was then performed. After i.v. preload with lactated Ringer's solution 20 ml kg^{-1}, 0.5% hyperbaric bupivacaine 2.0 ml and fentanyl 15 μg were injected intrathecally with the patient in the right lateral position. The patient was then turned supine with left lateral tilt. Preparation and surgery started after checking that the level of the block was adequate. Our contingency for patients in the air group who developed a pulse oximetry reading of <94% was to increase the $F\text{I}_{O_2}$ to 28%. Hypotension, defined as a decrease in systolic arterial pressure of more than 20% from baseline or to less than 100 mm Hg,[6] was treated with i.v. boluses of ephedrine, as required. Nausea and vomiting were treated with metoclopramide 10 mg i.v. once hypotension had been excluded. The times from starting oxygen supplementation to delivery, skin incision to delivery (I–D) and uterine incision to delivery (U–D) were recorded using a stopwatch. After delivery, a blinded paediatrician assessed Apgar scores.

Maternal arterial (MA) blood samples were taken before the start of anaesthesia, with the patient breathing room air, and at 5-min intervals after applying the facemask until delivery of the baby. The investigator who performed all the blood analyses was blinded to the $F\text{I}_{O_2}$ and did not participate in patient care. Fetal umbilical arterial (UA) and venous (UV) blood samples were collected from a segment of umbilical cord, double-clamped before the infant's first breath. For each blood sample, blood gas analysis was performed immediately using a Corning 278 pH/blood gas analyser (Medfield, MA, USA). The remainder of the sample was centrifuged and the plasma was stored at −70°C for subsequent batch analysis for 8-isoprostaglandin $F_2\alpha$ (8-isoprostane), malondialdehyde (MDA), organic hydroperoxides (OHP) and metabolites of oxidative purine metabolism.

Plasma concentrations of MDA were estimated as reactive substances by a thiobarbituric acid adduction method as described by Richard and colleagues[7] with partial modification.[8] An enzymatic technique[9] was used to determine OHP. For the measurement of purine and pyrimidine metabolites, the concentrations of cytosine, uracil, cytidine, hypoxanthine, xanthine, uric acid, guanine, uridine, thymine, adenine, inosine, guanosine and adenosine were determined simultaneously by reverse-phase high-performance liquid chromatography modified partially from previously described techniques.[10] Total free and esterified 8-isoprostane was estimated with an enzyme immunoassay kit (Cayman Chemical, Ann Arbor, MI, USA) with a precision of 97.9%.

Statistical analysis

In a previous study, we found that the mean and standard deviation of UA plasma concentrations of MDA and OHP during elective Caesarean section were 0.580 (0.029) and 0.135 (0.058) μmol l^{-1} respectively.[11] Using these data, we calculated that a sample size of 22 patients in each group yielded >80% power to detect a difference of 0.05 μmol l^{-1} of MDA or OHP with a type I error probability of 0.05. Data were tested initially for equality of variances using Levene's test, and the normal probability plot was used subsequently to test for normality. On the basis of these findings, statistical comparison was performed using either Student's t-test or the Mann–Whitney U-test. The χ^2 test was used to compare equality of proportions, and the association between Pa_{O_2}, 8-isoprostane MDA and OHP in maternal and umbilical blood was compared using the Spearman rank correlation. Results are presented as mean and standard deviation or median and range where appropriate. $P<0.05$ was considered significant.

Results

All patients completed the study. The indications for surgery are summarized in Table 1. Maternal and fetal

Table 2 Maternal characteristics and arterial blood gas (ABG) data. Mean (SD), median (range). n.s. = not significant

	Air group (n=22)	**Oxygen group** (n=22)	P
Characteristics			
Age (yr)	31.5 (23–38)	32.1 (25–43)	n.s.
Height (cm)	154.7 (4.7)	155.9 (4.7)	n.s.
Weight (kg)	64.2 (6.6)	66.8 (7.7)	n.s.
ABG baseline			
pH	7.42 (0.02)	7.43 (0.02)	n.s.
P_{O_2} (kPa)	14.3 (2.1)	14.8 (9.9)	n.s.
P_{CO_2} (kPa)	4.1 (0.3)	4.0 (0.4)	n.s.
Base excess (mmol litre^{-1})	−2.4 (1.3)	−2.5 (1.4)	n.s.
ABG during surgery			
pH	7.43 (0.04)	7.44 (0.03)	n.s.
P_{O_2} (kPa)	14.3 (2.5)	31.8 (5.9)	<0.001
P_{CO_2} (kPa)	4.3 (2.3)	4.0 (2.4)	n.s.
Base excess (mmol litre^{-1})	−1.8 (1.4)	−2.0 (1.5	n.s.
ABG at birth			
pH	7.41 (0.04)	7.43 (0.03)	n.s.
P_{O_2} (kPa)	14.2 (1.9)	30.0 (6.3)	<0.001
P_{CO_2} (kPa)	4.4 (0.7)	4.1 (0.5)	n.s.
Base excess (mmol litre^{-1})	−2.1 (1.8)	−2.6 (1.9)	n.s.

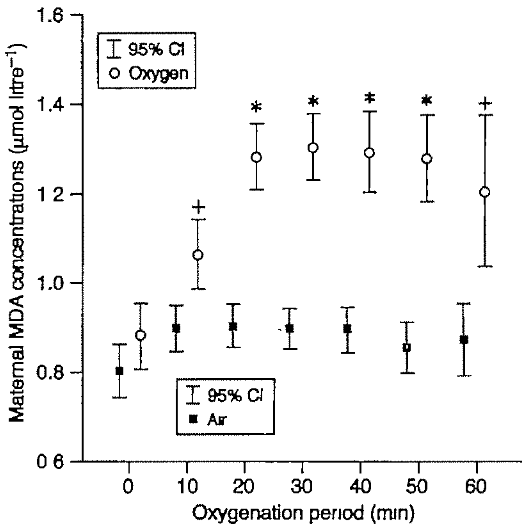

Fig 1 Maternal plasma concentrations of malondialdehyde at 10-min intervals. Data are mean (95% confidence interval) concentration for each interval after commencement of oxygen supplementation $^{+}P<0.05$, $^{*}P<0.001$.

characteristics, duration of oxygen exposure, timed intervals to delivery from skin incision (I–D) and uterine incision (U–D) were similar between groups (Tables 2 and 3). No treatment for arterial desaturation was required and the incidence of hypotension was similar in the two groups.

Maternal blood analysis

The MA blood gases data are summarized in Table 2. Baseline parameters while breathing room air were similar. Compared with the air group, the oxygen group had greater arterial Pa_{O_2}intraoperatively [mean 31.8 (SD 5.9) *vs* 14.3 (2.5) kPa, mean difference 17.5 kPa, 95% confidence interval 16.3–18.4 kPa, $P<0.001$] and at delivery [mean 30.0 (6.3) *vs* 14.2 (1.9) kPa; mean difference 15.8 kPa, 95% confidence interval 12.9–18.7 kPa, $P<0.001$]. There were no differences in the other parameters (pH, Pa_{CO_2} and base excess). Mean intraoperative plasma concentrations of MDA were greater in the oxygen group than in the air group [1.26 (0.22) *vs* 0.89 (0.16) µmol l^{-1}, $P<0.05$]. The increase in MDA was significant within 10 min of exposure to the higher F_{IO_2} (Fig. 1) and at birth both isoprostane and MDA were higher in the oxygen than in the air group (Table 4). The concentrations of OHP and purine metabolites were similar between groups.

Apgar scores and umbilical cord blood analysis

Apgar scores were similar between groups, with all scores >7 at 1 min and >9 at 5 min. The umbilical cord blood gases are summarized in Table 3. Umbilical venous Pa_{O_2} was greater in the oxygen than in the air group [4.8 (1.0) *vs* 4.0 (1.4) kPa; mean difference 0.7 kPa, 95% confidence interval 0.0–1.5 kPa, P=0.04]. There was a positive correlation between UV Pa_{O_2} and maternal arterial Pa_{O_2} at delivery (r=0.516, $P<0.001$) (Fig. 2). Other umbilical venous and arterial blood gas variables were similar between groups.

Plasma concentrations of lipid peroxides were greater in both the UA and UV samples of the oxygen than in the air group (Table 4). In both groups, there was a positive correlation between the MA Pa_{O_2} and the UV concentrations of 8-isoprostane (r=0.87, $P<0.001$) (Fig. 3), OHP (r=0.61, $P<0.001$) (Fig. 4) and MDA (r=0.56, $P<0.001$) (Fig. 5). Paired comparison of plasma concentrations of MDA showed significant increases as early as in the first 10 min after starting oxygen supplementation (Fig. 1). A weak correlation was found between the MA and the UV concentrations of MDA (r=0.38, $P<0.05$) and OHP (r=0.29, P=0.61), and plasma UA and UV concentrations of purine and pyrimidine metabolites were similar between groups.

Discussion

The rationale for providing supplementary oxygen to the mother during Caesarean section is to optimize neonatal outcome.[2–5] Although several previous studies have shown benefits, such as improved UA Pa_{O_2}, UV Pa_{O_2}, acid–base status and enhanced fetal adaptation, most of these studies were based on general anaesthesia. Therefore, it may not be valid to extrapolate their findings to spinal anaesthesia. Nonetheless, giving oxygen supplementation to patients undergoing Caesarean section under regional anaesthesia is commonly advocated.[12] Ramanathan and colleagues reported that UV Pa_{O_2} was improved when parturients receiving epidural anaesthesia breathed increased F_{IO_2} (47–100% F_{IO_2}).[5] However, in a more recent study, Kelly

Table 3 Fetal characteristics, timed intervals, Apgar scores and umbilical cord blood gas data Values are mean (SD), median (range) or number (%) I–D = interval from skin incision to delivery. U–D = interval from uterine incision to delivery n.s = not significant

	Air group (*n*=22)	**Oxygen group** (*n*=22)	***P***
Fetal characteristics			
Maturity (wk)	38.1 (37–40 3)	38.1 (37–39 4)	n.s.
Birth weight (kg)	3 08 (2 9–3 7)	3 14 (2 6–3 9)	n.s
Timed intervals			
I–D (min)	7.2 (6 2–7 6)	7.5 (6 3–8 1)	n s
U–D (s)	68 (52–75)	69 (55–85)	n s.
Duration of O_2 exposure (min)	52 7 (35–70)	53 2 (33–150)	n s
Apgar score			
1 min	9 (7–10)	9 (8–10)	n s
5 min	10 (9–10)	10 (9–10)	n s
<7 at 1 min	0 (0%)	0 (0%)	n.s
<7 at 5 min	0 (0%)	0 (0%)	n s
Umbilical arterial blood gases			
pH	7 25 (0.09)	7.24 (0.09)	n.s.
P_{O_2} (kPa)	2.4 (0 6)	2.4 (0 8)	n s
P_{CO_2} (kPa)	7.2 (1.7)	7 5 (1.38)	n.s.
Base excess (mmol $litre^{-1}$)	–4 6 (3 4)	–4 7 (3.8)	n s.
Umbilical venous blood gases			
pH	7 29 (0.08)	7.30 (0.07)	n.s.
P_{O_2} (kPa)	4.0 (1.4)	4 8 (1 0)	<0 05
P_{CO_2} (kPa)	6 1 (0 9)	6.0 (0.8)	n s.
Base excess (mmol $litre^{-1}$)	–4.4 (3 7)	–4 2 (3 3)	n s

and colleagues reported that parturients who received spinal anaesthesia had no maternal oxyhaemoglobin desaturation despite deterioration in respiratory mechanics, and that administration of 35% oxygen did not improve UV Pa_{O_2}.[1] In our study, we found that administration of 60% FI_{O_2} to parturients undergoing spinal anaesthesia resulted in a modest increase in UV Pa_{O_2}. However, because the magnitude of this increase was relatively small and because there was no difference in neonatal outcome, the clinical advantage of administering a high FI_{O_2} compared with air routinely to elective cases is questionable, provided that continuous monitoring with pulse oximetry is available. Moreover, administration of a high FI_{O_2} was associated with increased free radical activity in both the mother and fetus.

Direct detection of free radicals is extremely difficult because of their brief lifespan. Thus, in our study we measured lipid hydroperoxides, the products of attack by free radicals on polyunsaturated fatty acids, as 'footprints' of free radical activity.[13 14] Isoprostanes, formed by non-enzymatic oxygenation of arachidonic acid in membrane phospholipids, are highly specific as markers for *in vivo* oxidative stress.[15] The best-characterized isoprostane is 8-isoprostaglandin $F_2\alpha$ (8-isoprostane), which is abundant in plasma and urine. MDA and OHP concentrations are less specific, and can be influenced by the extent of prostaglandin metabolism as well as by free radical activity.

Pathological generation of free radicals commonly involves one of several possible pathways. We have shown previously an association between increased concentrations of lipid peroxides and prolonged labour, fetal distress, oligohydramnios and tight nuchal cord entanglement.[16–21] In these conditions, free radicals are generated via the pathways involving hypoxic stress and ischaemia–reperfusion injury. During hypoxia, xanthine dehydrogenase is converted into xanthine oxidase. After reperfusion, xanthine oxidase catalyses the formation of hydroxyl free radicals from the breakdown of purine metabolites, xanthine and hypoxanthine.[22] Thus, an accompanying increase in purine metabolites is a co-marker of ischaemia–reperfusion injury. Hyperoxia *per se* generates free radicals via an alternative pathway involving direct mitochondrial electron transfer, with no concurrent formation of purine metabolites. Thus, in our study, because there was no increase in purine metabolites, the most likely mechanism for the generation of free radicals was maternal hyperoxia.[23 24]

Table 4 Maternal and umbilical lipid peroxide concentrations Values are mean (SD); units are µmol $litre^{-1}$ n.s. = not significant; N/A=not available

	Air group (*n*=22)	**Oxygen group** (*n*=22)	***P***
Maternal arterial (baseline)			
Isoprostane	118 8 (21.3)	127 4 (28 5)	n.s.
Malondialdehyde	0.89 (0.13)	0 93 (0.12)	n.s.
Organic hydroperoxides	0 13 (0 02)	0 14 (0 02)	n s
Maternal arterial (during surgery)			
Isoprostane	N/A	N/A	N/A
Malondialdehyde	0 89 (0.16)	1 26 (0.22)	<0 001
Organic hydroperoxides	0.14 (0.02)	0.14 (0 03)	n.s
Maternal arterial (at birth)			
Isoprostane	121 8 (23.8)	200 6 (54.3)	<0 001
Malondialdehyde	0 89 (0.16)	1 12 (0 32)	<0 05
Organic hydroperoxides	0.14 (0.02)	0.14 (0 02)	n s
Umbilical venous			
Isoprostane	135.3 (66.7)	403.0 (100 4)	<0 001
Malondialdehyde	0.47 (0.13)	0 78 (0 16)	<0 05
Organic hydroperoxides	0 15 (0 05)	0.50 (0 17)	<0 001
Umbilical arterial			
Isoprostane	122 1 (73 4)	215.2 (92.7)	<0 001
Malondialdehyde	0 40 (0.06)	0 48 (0.10)	<0 001
Organic hydroperoxides	0.18 (0 09)	0.39 (0 10)	<0 001

Lipid peroxide concentrations were much greater in UV than in UA blood, suggesting that the main site of free radical activity was the placenta, the interface where hyperoxia occurs. Concentrations of 8-isoprostane were greater in umbilical than in maternal blood, implying generation in the fetoplacental unit. Concentrations of MDA were greater in maternal than in umbilical blood, but were unlikely to be the result of placental transfer because of the weak correlation between the maternal and umbilical concentrations.[11] In the maternal blood, the increase in lipid peroxides results from the net effect of lipid peroxidation and free radical scavenging throughout the body, whereas the increase in the umbilical vein reflects the origin more specifically at the placenta. A positive correlation between maternal arterial Pa_{O_2} and the umbilical lipid peroxide concentration suggests a direct relationship

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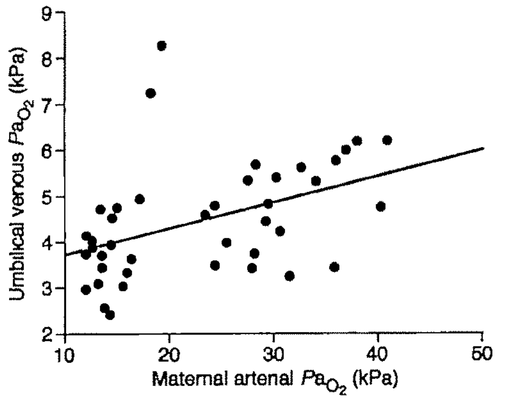

Fig 2 Scatter-plot of maternal arterial Pa_{O_2} at delivery and umbilical venous Pa_{O_2}. Data from air and oxygen groups are presented. r=0 516, P<0 001

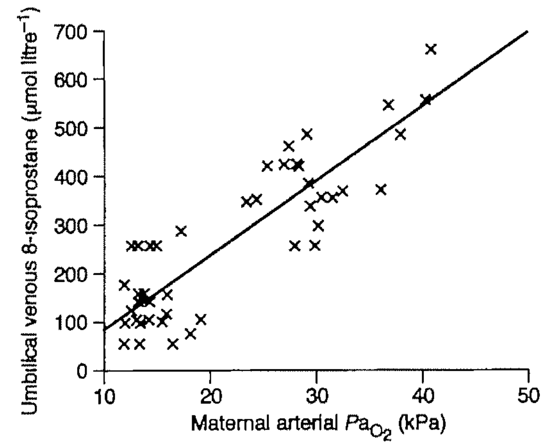

Fig 3 Scatter-plot of maternal arterial Pa_{O_2} at delivery and umbilical venous concentration of 8-isoprostane Data from air and oxygen groups are presented. r=0.870, P<0.001.

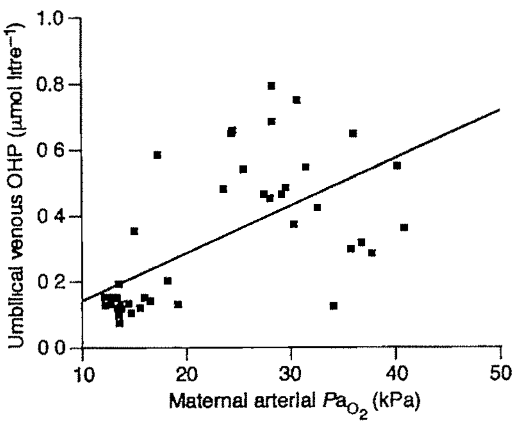

Fig 4 Scatter plot of maternal arterial Pa_{O_2} at delivery and umbilical venous organic hydroperoxides. Data from air and oxygen groups are presented. r=0 611, P<0 001.

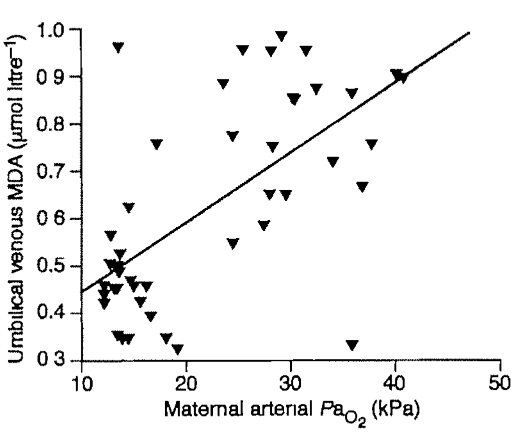

Fig 5 Scatter plot of maternal arterial Pa_{O_2} at delivery and umbilical venous malondialdehyde Data from air and oxygen groups are presented. r=0 556, P<0.001

between the oxygen partial pressure and the extent of free radical activity in the fetoplacental unit.

The clinical relevance of the increase in free radical activity we found in the oxygen group is uncertain. Although clinical effects were not apparent in our study, free radicals cause depletion of intrinsic antioxidant systems and could weaken the infant's ability to withstand any subsequent neonatal insult. MDA, a product of lipid peroxidation, is toxic because of its ability to form disulphide bridges across nucleotide or amino acid chains,[25] and also causes immunosuppression by inhibiting lymphocytic activity.[26] Our study was confined to healthy, elective cases with uncomplicated pregnancies. Although we found no difference in neonatal outcome between groups, Apgar scores can only demonstrate very gross changes, and in elective low-risk cases maternal hyperoxygenation would not be expected to have a significant effect on an outcome that is already likely to be favourable.

Conversely, the relative benefit of administration of a high $F\text{I}_{O_2}$ where there is fetal compromise is unknown. It has been shown that hyperoxia increases the formation of free radicals, which may exacerbate tissue damage in ischaemia reperfusion injury.[23 24 27 28] Hyperoxia mediates tissue injury in bronchopulmonary dysplasia, retinopathy of prematurity, persistent ductus arteriosus, necrotizing enterocolitis and intracranial haemorrhage.[29–31] Furthermore, when oxygen was compared with air during neonatal resuscitation, a poorer outcome resulted because of the generation of free radicals.[32 33] Therefore, further investigation is required to clarify the relative advantages and disadvantages of high $F\text{I}_{O_2}$ in emergency Caesarean section when there is fetal distress, as high $F\text{I}_{O_2}$ may increase fetal oxygenation, but may also exacerbate ischaemia–reperfusion injury in the fetus.

Patient comfort is also an issue. This has led to the investigation of different methods of oxygen delivery during Caesarean section.[34] In our experience, parturients sometimes complain of discomfort from wearing oxygen facemasks, which may be unnecessary given the questionable benefit of supplementary oxygen.

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Model-based administration of inhalation anaesthesia. 3. Validating the system model

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Background. We quantified the predictive performance of our computer model of the administration of inhalation anaesthesia from a Datex-Ohmeda Modulus CD circle-absorber system.

Methods. In 50 patients, desflurane anaesthesia was maintained with a fresh-gas flow (FGF) of 0.5 litres min^{-1} of both nitrous oxide and oxygen, preceded by fast (n=14) or slow (n=36) induction: FGF greater than total ventilation, Group F; FGF equal to 1.0 litres min^{-1}, Group S. The two versions of the model studied differed in the size of their inter-tissue diffusion, as 0 (version 1) and 3% (version 2) of the cardiac output was shifted from the viscera to adipose tissue. Model performance was judged by comparing measured and predicted gas concentrations in terms of three variables for each gas concentration in each patient: root mean squared error (rmse=total error), bias (mean predicted – measured) (systematic error), and scatter (error around bias). These variables were then averaged over all patients. These measures were calculated overall, and separately for each group and each stage (1=induction or 2=maintenance).

Results. Model predictions were in reasonable to very good agreement with clinically obtained data. Version 2 performed better than version 1. Differences between groups were not demonstrated. The model performed better for stage 2, but only for desflurane. In group S, results (mean (SD); as percentages of the measured values for nitrous oxide, oxygen and desflurane) in the order rmse, bias, and scatter were for end-tidal concentrations of nitrous oxide: 8 (4), 8 (5), 2 (1)%; oxygen: 11 (4), –10 (6), 2 (1.1)%; nitrogen: 0.9 (0.6), –0.8 (0.6), 0.2 (0.1) vol%; carbon dioxide: 1.8 (0.6), 1.8 (0.6), 0.2 (0.1) vol%; desflurane, stage 2: 8 (4), 4 (7), 4 (2)%, *vs* 15 (6), –10 (8), 9 (4)% for stage 1.

Conclusion. Administration of inhalation anaesthesia can be based on version 2 of this model, but must be guided by active monitoring.

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We have developed a system model for the administration of inhalation anaesthesia from a particular circle-absorber breathing system with a standing bellows.[1] The model includes almost all gases present in the system, and will handle a wide range of fresh gas flows (FGF). We have shown[1] that its predictions agree reasonably well with some published clinical data and that it can reproduce well-known phenomena in the administration of inhalation anaesthesia.[2]

This paper presents a prospective comparison with clinical data and aims to quantify the predictive performance of the model. General anaesthesia with desflurane and nitrous oxide in oxygen was administered to 50 patients under low-flow conditions. We retrospectively compared the predicted inspired and end-tidal concentrations of desflurane, nitrous oxide, oxygen, carbon dioxide, and nitrogen with those measured in each patient. Two versions of the model were formulated. One version (1) is the basic

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model;[1] another (2) accounts for large-scale diffusion between body compartments.[3]

Patients and methods

Anaesthetic management

Fifty consenting patients (ASA physical status I and II) were studied after approval of the Institutional Ethics and Research Committee. They were to undergo elective eye surgical procedures expected to last at least 30 min. Diazepam 10 mg and droperidol 2.5 mg were given orally 1 h before surgery. An i.v. catheter was inserted and basic monitoring (ECG, automatic non-invasive arterial pressure (NIBP), pulse oximetry) established. NIBP was measured with 1-min intervals for 20–30 min and a 3–5-min interval thereafter.

The anaesthetic breathing system (Fig. 1 in reference 1) was filled with air by flushing it with 9 litres min^{-1} medical air for 3 min. When the mask was applied to the face of the patient, fresh gas was switched from air to oxygen to perform denitrogenation and pre-oxygenation. Fentanyl 3 $\mu\text{g kg}^{-1}$ i.v. was given. Two minutes later, anaesthesia was induced with an i.v. dose of propofol sufficient to obtund the eyelash reflex and rocuronium 0.5 mg kg^{-1} i.v.. The patient's lungs were ventilated manually by mask for 2 min, using a FGF of 12 litres min^{-1} (nitrous oxide:oxygen, 1:1); an increment of propofol of 20–40 mg i.v. was then given, according to body mass, and changes in the NIBP as a result of inducing anaesthesia. After a further 30 s, topical anaesthesia of the larynx with 2–4 ml of lidocaine 4.3% spray was performed, the patient's trachea was intubated with a cuffed tube, and the cuff was inflated.

The patient was reconnected to the breathing system and the ventilator, and the lungs were artificially ventilated with a FGF of 9 litres min^{-1} (nitrous oxide:oxygen, 2:1) until the end-expiratory nitrogen concentration was less than 2 vol% (vol% is used for concentrations to avoid confusion with the per cent unit for the performance measures), or for a maximum of 10 min. Subsequent treatment depended on allocation to group S ('slow scheme') or group F ('fast scheme'). Patients were not deliberately placed in one or the other group, but an increased proportion of patients (5:2, eventually) were assigned to group S (to achieve greater clinical experience with low-flow conditions).

In group S (n=36), the initial total FGF was set to 1 litre min^{-1} (i.e. 0.5 litres min^{-1} each of nitrous oxide and oxygen). Reducing the FGF from 9 to 1 litre min^{-1} necessitated adjustment of tidal volume because delivered tidal volume depended on the rate of FGF into the standing bellows ventilator.[4 5] Once the total ventilation was stable, the vaporizer was set to deliver 12 vol% desflurane until its end-expired concentration was appropriate as judged by the attending anaesthetist (J.L.). Then, for the second stage, the vaporizer setting was reduced to 1 vol% above the target end-expired concentration, while the FGF was kept unchanged.

In group F (n=14), the initial total FGF exceeded at least the assumed alveolar ventilation, or was even greater than total ventilation, and the vaporizer was initially set to deliver 6 vol% desflurane until its end-expired concentration was appropriate as judged by the attending anaesthetist (J.L.). The second stage was the same as in group S. Each of the schemes reflected one out of two dosing strategies commonly used in the clinical environment.

During maintenance, we modified desflurane administration to provide adequate anaesthesia. We therefore carefully monitored the patient's response to surgery by assessment of NIBP, heart rate, and heart rate variability judged by ear with the aid of pulse oximetry, and also end-tidal desflurane concentration. Extra fentanyl (0.05–0.1 mg) was given according to clinical needs. The end-tidal carbon dioxide concentration was maintained at 3.6–4.6 vol%. Desflurane was purchased from Pharmacia Nederland B.V. (Woerden).

Instrumentation

The anaesthetic equipment consisted of a Modulus CD anaesthesia system (Ohmeda, Madison, USA), which is routinely used in the operating theatres for ophthalmic surgery. The anaesthetic breathing system comprised a soda-lime canister (part of the Ohmeda GMS (Gas Management System) Absorber), two 1-m corrugated tubes in each limb, a water trap in each limb, and a Y-piece. The switch in the GMS allowed swift alternation between reservoir bag and ventilator: (i) a 2-litre bag at the end of 1-m length of corrugated tubing was used for spontaneous breathing and manual ventilation by mask; and (ii) a standing bellows ventilator (Ohmeda 7850) supported artificial ventilation of the lungs. A scheme of the breathing system with an internal volume of 6.6 litres, as used during artificial ventilation, was given in Figure 1 of reference 1. Leaks in the circuit were detected by plugging the Y-piece, pressurizing the breathing system to 4 kPa, and observing the volume and pressure gauge; a gas leak up to 60 ml min^{-1} was accepted. Desflurane was delivered in all patients by the same Ohmeda Tec 6 vaporizer. The accuracy of the Rotameters (oxygen, nitrous oxide, air) was checked against a bubble flow meter. The expiratory volumes were measured with an Ohmeda volume monitor; the turbine vane transducer sensor has an accuracy of ±5%.[6]

A respiratory mass spectrometer (QP 9000) was located in a nearby room. One of its two inlet ports was connected to a 2-m inlet probe, the other to a valve box which sampled via 30-m nylon probes,[7 8] at 60 ml min^{-1}, either at the Y-piece or from the FGF. Switching between the two inlet ports was done by pinch valves incorporated in the mass spectrometer, and between the long probes by a pair of electromagnetic valves. The hospital vacuum was used to draw continuously a matching 60 ml min^{-1} from whichever 30-m probe was not connected to the mass spectrometer.

Normally the mass spectrometer continuously sampled gas from the Y-piece but, each time the setting of the vaporizer was changed, it was switched to sample fresh gas for 40 s.

The mass spectrometer was calibrated once or twice per day (morning and afternoon list) with just the 2-m inlet probe according to a procedure recommended by the manufacturer (CaSE, Gillingham, UK) using two gas mixtures of known composition. In addition, before starting each list we verified the mass spectrometer's calibration with one of the long probes (both had same geometry) using room air and the same two calibration gas mixtures: (i) 1 vol% argon, 5 vol% carbon dioxide, 44 vol% oxygen in nitrous oxide; and (ii) 4 vol% desflurane, 44 vol% oxygen in nitrogen (AGA Gas, Amsterdam, The Netherlands). Six channels were tuned to the mass-charge ratios required to measure nitrogen (28), oxygen (32), carbon dioxide (12), nitrous oxide (30), argon (40), and desflurane (51). An eight-channel thermal array recorder (Nihon Kohden RTA 1300) running at 10 mm min^{-1} recorded the mass spectrometer signals.

A personal computer system located in the operating theatre processed the signals from the mass spectrometer (12-bit analogue-to-digital board (Keithley Metrabyte, USA)), was allowed to operate the switching mechanism for the valves, and recorded all variables acquired by the Modulus CD anaesthesia system (e.g. expiratory ventilation) from its RS232 output port. The data acquisition software was developed with the aid of ASYST™ (Keithley Metrabyte). On-line analysis of the respiratory waveforms allowed continuous monitoring of the actual inspiratory and end-expired concentrations of nitrogen, oxygen, carbon dioxide, nitrous oxide, argon, and desflurane. Every 10-s the last inspiratory and end-expired concentrations of these gases were saved on hard disk for further data processing.

The model

Versions

Version 1 is the basic model that was quantified earlier.[1] For desflurane it uses the tissue/gas partition coefficients reported by Yasuda and colleagues,[9] and a blood–gas partition coefficient of 0.52 as reported by Lockwood and co-workers.[10] Version 2 uses one of the amendments that Allott and colleagues[11] made to their basic model as a simple means of mimicking inter-tissue diffusion. Part of the cardiac output was, therefore, redirected from the viscera, i.e. kidneys, heart, brain, and liver, to the adipose tissue. In successive simulation runs, the total fraction redirected cardiac output (f_R) was increased, with steps of 0.01, until the cumulative uptakes of desflurane and isoflurane predicted by our model agreed closely with those reported by Hendrickx and co-workers.[12] Their experimental conditions were mimicked in the way already described.[1] As the sum of the fractions of cardiac output to the viscera in version 1 is 0.76, the fractions for version 2 were obtained by multiplying those in version 1 by $(0.76-f_R)/0.76$.

Adapting the model to experimental conditions

Clinically important details were incorporated into the original model with the aim of performing this validation study. During the process of intubation there is a period of apnoea that may be short but also rather lengthy in case of a more difficult intubation. It is virtually impossible to fully describe the impact of removing the facemask and intubating the trachea on the composition of the gas mixture in the lungs and the anaesthetic breathing system. The model therefore assumed that, during apnoea, alveolar ventilation was zero and gas exchange continued across the alveolo-capillary membrane.

With a leak measured to be $\leqslant 60$ ml min^{-1} at a continuous breathing-system pressure of 4 kPa, plus a sample flow of 60 ml min^{-1}, careful consideration of detail led us to conclude that, in use, a net loss as 75 ml min^{-1} of inspired mixture would be a good estimate of the effective loss. (Accuracy is minimally influenced by this legitimate assumption.)

The model also accounted for the sample flow drawn off continuously by the hospital vacuum at the common gas outlet ($\dot{V}_{sf}$). If $\dot{V}_{F_i}$ was the FGF for each component i (nitrogen, oxygen, nitrous oxide, or desflurane), then its effective FGF entering the circle system was given as:

$$\dot{V}_{F_i}\ (\text{effective}) = \dot{V}_{F_i}\left(1 - \frac{\dot{V}_{sf}}{\sum_i \dot{V}_{F_i}}\right)$$

The ventilation in the model was matched to that measured for each patient as follows. A target value for the 'ideal' alveolar carbon dioxide tension ($P_{A_{CO_2}}$, assumed equal to Pa_{CO_2}) was obtained from: (i) the ventilation measured (averaged over the period of administration of desflurane); (ii) a chosen value of 50% for wasted ventilation;[1] and (iii) a specific, rearranged form of equation (24) in Appendix 2 of reference 1. The value obtained was used by the model to calculate alveolar ventilation (see below).

Simulated end-expired tensions were calculated according to Landon and co-workers[13] from the 'ideal' alveolar (P_A) and dead space (=inspired; P_I) tensions predicted by our model: $P_{E'}=(1-d)P_A+dP_I$. For each patient, the 'dilution factor' d (the fraction of dead space gas in end-expiratory gas)[13] was deduced from the arterial and end-expired carbon dioxide tensions: $d=(Pa_{CO_2}-P_{E'}{}_{CO_2})/Pa_{CO_2}$. Assuming that $Pa_{CO_2}-P_{E'}{}_{CO_2}=0.533$ kPa (see discussion) and as $Pa_{CO_2}=P_{A_{CO_2}}$, it follows that $d=0.533/P_{A_{CO_2}}$.

Comparing measurements with predicted values

This was a three-step process. During step one, the model input was generated. The model input consisted of the anthropometric data (age, sex, body weight, and height), the FGF rates (air, oxygen, and nitrous oxide),

Table 1 Definitions of predictive performance measures C_p and C_m = pair of predicted and measured concentrations (one pair for each time period of 10 s) n = number of measurements per gas per patient in a defined period of time, pe_i is the i-th prediction error, and me = mean prediction error

Performance measure	Unit	Mathematical definition	Remarks
Prediction error	%	$pe = \frac{C_p - C_m}{C_m} \times 100$	Per pair of predicted and measured values for desflurane, nitrous oxide, or oxygen
	vol%	$pe = C_p - C_m$	Per pair of predicted and measured values for nitrogen or carbon dioxide
Root mean squared error (rmse)	% or vol%	$\sqrt{\frac{1}{n}\sum_{i=1}^{n} pe_i^2}$	Identifies the total error budget; has no sign, = $\sqrt{\text{bias}^2 + \text{scatter}^2}$
Bias	% or vol%	$me = \frac{1}{n}\sum_{i=1}^{n} pe_i$	Represents the systematic component of the error; has a direction (or sign) and a magnitude
Scatter	% or vol%	$\sqrt{\frac{1}{n}\sum_{i=1}^{n}(pe_i - me)^2}$	Indicates the dispersion of the errors (pe) around their mean (me), has no sign

the desflurane concentration in the FGF (the measured signal averaged over 5 s), the target value for the ideal alveolar carbon dioxide tension, and the period of apnoea during intubation. Throughout step two, our model generated the predicted time courses of the inspired and end-expired concentrations of desflurane, nitrous oxide, oxygen, carbon dioxide, and nitrogen by running the model in a Tutsim™ simulation program (Meerman Automation, Neede, The Netherlands). In the final step three, the differences between predicted and measured concentrations (the 'predictive performance measures', *vide infra*) were analysed in a Mathcad (version 7) worksheet (Mathsoft, Bagshot, Surrey, UK).

Predictive performance measures

Definitions

The summary measures that served to determine the predictive performance of the model are defined in Table 1. The prediction error (pe) is the difference between a predicted and a measured concentration; pe can be expressed as a vol% difference (nitrogen and carbon dioxide) or as a percentage of the measured value (N_2O, O_2, desflurane). Prediction error and squared prediction error (pe^2) are calculated for each time period of 10 s. These two quantities are used to provide the following three predictive performance measures.

1. Root mean squared error (rmse). The mean squared error (mse) is the average of the squared prediction errors. Rmse is defined as $\sqrt{\text{mse}}$ and is a measure of the total error budget for an individual patient in a defined period of time. Rmse is *not* influenced by the signs of the prediction errors. Rmse can be decomposed into two terms: rmse=$\sqrt{\text{bias}^2 + \text{scatter}^2}$ (Table 1).
2. Bias (me), that is the average of the prediction errors for an individual patient, is a measure of the systematic component of error. It can be either positive or negative, thus indicating over- or under-prediction, respectively. It does *not* provide information about the typical size of the prediction error if there are both under- and over-predictions in an individual patient.
3. Scatter is a measure of the variation of the prediction errors for an individual patient around the mean (or bias) for that patient.

These three measures were calculated for the inspired and end-tidal concentrations of desflurane, nitrous oxide, oxygen, and nitrogen, and for the end-tidal concentration of carbon dioxide—a total of 3×9=27 performance measures for each patient, or 54 when calculated separately for stages 1 and 2.

Overall performance measures

'Overall' measures evaluate the whole period including stages 1 and 2, which ends at the moment when artificial ventilation was stopped. Each of 27 performance measures per patient were averaged over all patients to yield the three group overall performance measures for each of the nine gas concentrations.

Performance measures per stage and group

Each of the performance measures was also assessed separately for each stage (1 or 2) and group (S or F). Calculating the numerical averages of the 36 (group S) or 14 (group F) performance measures—one per patient and per

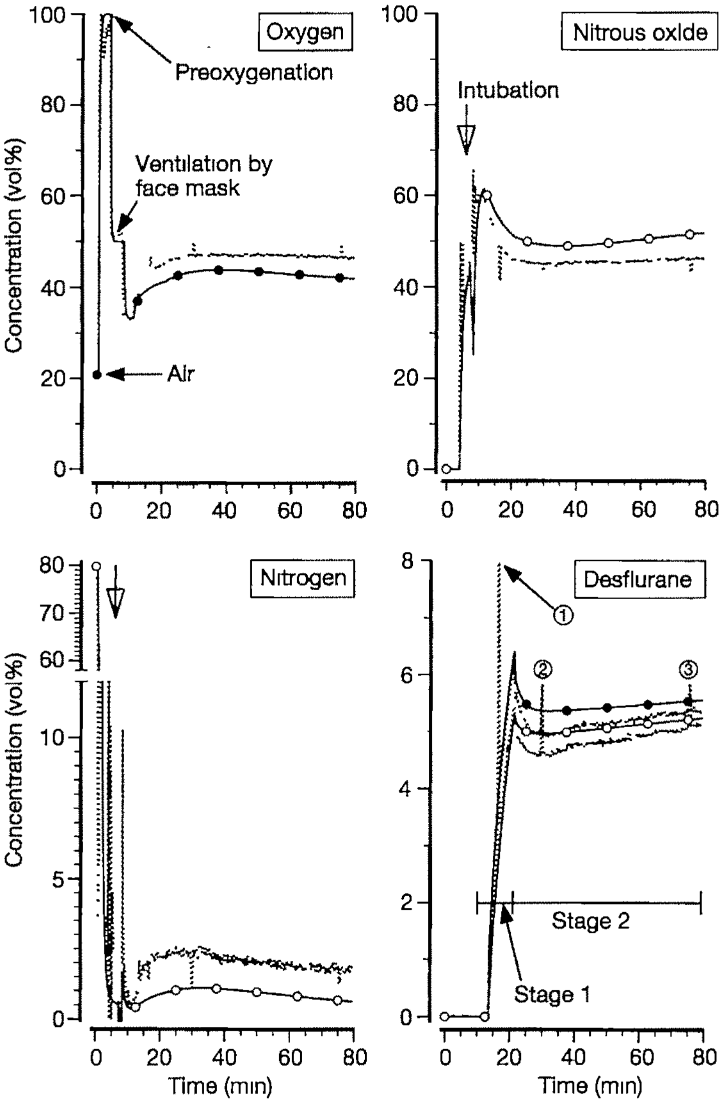

Fig 1 Measured and predicted (version 2) concentrations from a 44-yr-old female patient (weight 65 kg, height 1.58 m) for inspired oxygen, end-tidal nitrous oxide and nitrogen, and inspired and end-tidal desflurane. The following periods or events can be recognized: pre-oxygenation and denitrogenation; ventilation by face mask, intubation; period of 9 litres min^{-1} FGF, that is the period with 33% inspired oxygen. The 'deviation spikes' on the measured concentrations result from the three 40-s periods (encircled numbers 1, 2, and 3) during which fresh-gas is sampled by the respiratory mass spectrometer to measure the delivered desflurane concentrations Note that the delivered desflurane concentration (11.81 vol%) goes off scale at the first sampling period Stage 1 is the period of induction (vaporizer set to deliver 12 vol% desflurane in 0.5 litres min^{-1} of each of nitrous oxide and oxygen), and stage 2 is the maintenance period (vaporizer set to deliver 6 vol% desflurane in 0.5 litres min^{-1} of each of nitrous oxide and oxygen).

gas concentration—yielded the group performance measures for a gas concentration for each stage.

Performance measures per version

Performance measures were calculated once for version 1 and once for version 2 of the model. Figures 1 and 2 serve to illustrate the predictive performance measures. Figure 1 shows a selection of measured and predicted concentration–time profiles in a patient who was considered representative because she belonged to the largest group S, had average physical characteristics, and showed individual results in agreement with group results. Figure 2 illustrates the biases and scatters of end-tidal desflurane in the same patient.

Statistical analysis

Student's *t*-test for unpaired data was used to test the difference between the means of the duration of stage 1 in group S *vs* F; $P<0.05$ was considered statistically significant.

Results for each of the 27 (or 54) performance indicators, per version, were expressed as mean of all patients and SD between patients, except where otherwise stated.

The sign test was used to compare the predictive performance of version 1 with that of version 2. We therefore tested the hypothesis of whether the rmse for version 2 was closer to zero. The same hypothesis was tested for bias and scatter.

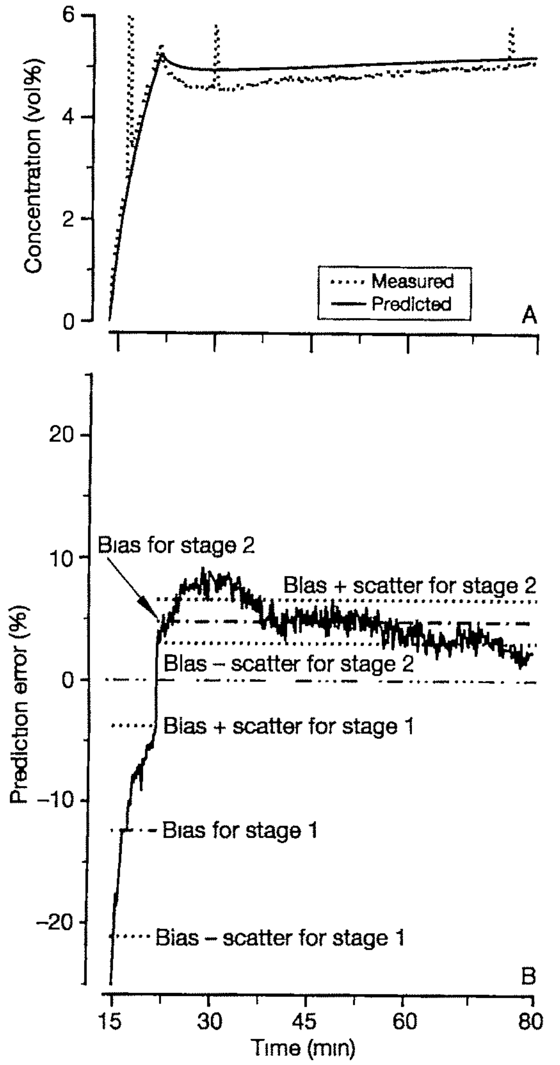

Fig 2 (A) Measured and predicted end-tidal desflurane concentrations obtained with version 2 in the same patient as in Figure 1 (B) Time course of the prediction errors. the *y*-axis extends from –25 to +25% with zero in the middle The overall rmse, bias, and scatter for end-tidal desflurane in this patient were 6.9, 3.1, and 6 1%, respectively For stage 1, rmse, bias, and scatter were 15.2, –12 4, and 8.7%, respectively, for stage 2, they were 5.1, 4.8, and 1.8%, respectively

Performance indicators were tested for differences between the means of stage 1 *vs* 2 (for each group) with a *t*-test for paired data, and group S *vs* F (for each stage) with a *t*-test for unpaired data. A $P<0.001$ (correction for multiple comparisons) was considered statistically significant; *n* denotes number of patients.

Results

Patients in group S and F had similar characteristics (Table 2). Figure 1 provides definitions for the stages and a visual impression of the quality of the predictions. Table 3 lists clinical details on settings of the FGF and vaporizer, as well as desflurane concentrations measured in the fresh gas. Slight variants of the schemes were applied in two patients of group S (in one patient 0.5 litres min^{-1} was used, and the vaporizer was set to 8 vol% in another) and in six patients of group F (4 vol% during stage 1 and 0.5 litres min^{-1} during stage 2; Table 3). Recovery from the anaesthetic was uneventful in all patients.

The intraoperative samples used for data analysis were from a total of more than 3000 min of anaesthesia. Table 4 lists the duration of the various measuring periods (no account was taken of the 40-s sampling periods needed to analyse the delivered desflurane concentration). Stage 1 was approximately 4 min shorter in group F *vs* S. The target concentration for desflurane was attained twice as fast in group F: 3.5 *vs* 7.1 min on average. The duration of stage 2 was equal for both groups (study design).

Model versions

Cumulative uptakes were computed for desflurane and isoflurane for the conditions used in the study by Hendrickx and co-workers;[12] these computed uptakes agreed closely with the measured values if f_R=0.03 (Fig. 3). Accordingly, version 2 uses the cardiac output partitioning listed in Table 5.

Overall predictive performance

Performance measures for desflurane, nitrous oxide, and oxygen have been expressed as percentages of the measured

Table 2 Patient characteristics in the total population and in the two groups. Values are mean (SD) [range] or number Patients with a body mass index (BMI) less than 20 kg m^{-2} are considered slender; patients with a BMI greater than 25 kg m^{-2} are designated obese Because of a BMI exceeding 34 kg m^{-2}, which is greater than mean BMI plus twice SD, two males (36 8 and 37.1 kg m^{-2}) and one female (34 6 kg m^{-2}) may be designated as outliers

	Total (*n*=50)	Group S (*n*=36)	Group F (*n*=14)
Gender (M/F)	33/17	24/12	9/5
Age (yr)	48 (16) [16–75]	47 (17) [16–75]	53 (13) [29–69]
Weight (kg)	76 (15) [49–115]	76 (14) [50–115]	74 (17) [49–105]
Height (m)	1 76 (0.10) [1 54–1 92]	1.77 (0 09) [1.54–1.90]	1 73 (0 12) [1 54–1.92]
BMI (kg m^{-2})	24 5 (4 5) [16.3–37.1]	24 5 (4 8) [16.3–37 1]	24.6 (3 7) [18 7–30 8]

Table 3 Clinical details on settings of FGF and vaporizer for the 50 patients, as well as desflurane concentrations (mean (SD)) measured in the FGF. In this table, patients are first categorized into the two groups (Slow and Fast, details see text), then in accordance with the settings of FGF and vaporizer during induction, and finally according to FGF settings and the *first* vaporizer setting during maintenance (in the order of increasing total FGF and vaporizer setting) *n*=number of patients. During maintenance, a second and third vaporizer setting was used in one*, two†, or three‡ patients

		Stage 1 (induction)				**Stage 2 (maintenance)**							
		FGF settings (litres min^{-1})		**Vaporizer setting** (vol%)	**Measured desflurane concentration** (vol%)	**FGF settings** (litres min^{-1})		**Vaporizer settings** (vol%)			**Measured desflurane concentration** (vol%)		
	n	**Oxygen**	**Nitrous oxide**			**Oxygen**	**Nitrous oxide**	**1st**	**2nd**	**3rd**	**1st**	**2nd**	**3rd**
S(low) group	1	0.3	0.2	12	12.0	0.3	0.2	6			5.98		
	1	0.5	0.5	8	7.69	0.5	0.5	4			4.17		
	9	0.5	0.5	12	11.87 (0.47)	0.5	0.5	4	2†	12*	4.22 (0.17)	2.3 (0.13)	12.0
	7	0.5	0.5	12	11.39 (0.29)	0.5	0.5	5	3* or 4†	3*	4.93 (0.11)	3.14 or 4.03 (0.04)	3.0
	18	0.5	0.5	12	11.96 (0.58)	0.5	0.5	6	4‡		6.35 (0.29)	4.31 (0.25)	
F(ast) group	1	1.5	3.0	6	6.17	0.5	0.5	6			6.15		
	2	2	3	6	6.26 (0.30)	0.3	0.2	6	3*		6.28 (0.08)	3.29	
	1	2	3	6	6.61	0.5	0.5	6	4		6.36	4.28	
	2	2	4	6	6.23 (0.08)	0.3	0.2	6	0*	3*	6.0 (0.08)	0.0	3.17
	3	2	4	6	6.31 (0.17)	0.5	0.5	6			6.03 (0.10)		
	1	3.5	3.5	6	6.82	0.5	0.5	6	4		6.36	4.32	
	1	2.5	5.0	4	4.41	0.5	0.5	4	2		3.94	2.19	
	1	2.5	5.0	6	6.73	0.5	0.5	4	3		4.39	3.47	
	1	2.5	5.0	6	6.63	0.5	0.5	6	5		6.1	5.21	
	1	3	5	4	4.35	0.5	0.5	4	2	3	3.97	2.25	3.13

Table 4 Duration of measuring periods (min) (mean (SD) [range]). *$P<0.001$ group S *vs* group F

	Overall (*n*=50)	Stage 1 Both groups (*n*=50)	 Group S (*n*=36)	 Group F (*n*=14)	Stage 2 (*n*=50)
Desflurane	60.8 (22.4) [37–176]	6.1 (3.0) [1.2–15.5]	7.1 (2.6) [2.7–15.5]	3.5 (2.2)* [1.2–10.0]	54.7 (22.4) [29.2–168.7]
Other gases	63.4 (22.3) [41–178]	8.7 (3.7) [2.5–19.8]	9.9 (3.5) [3.7–19.8]	5.7 (2.2)* [2.5–12.0]	54.7 (22.4) [29.2–168.7]

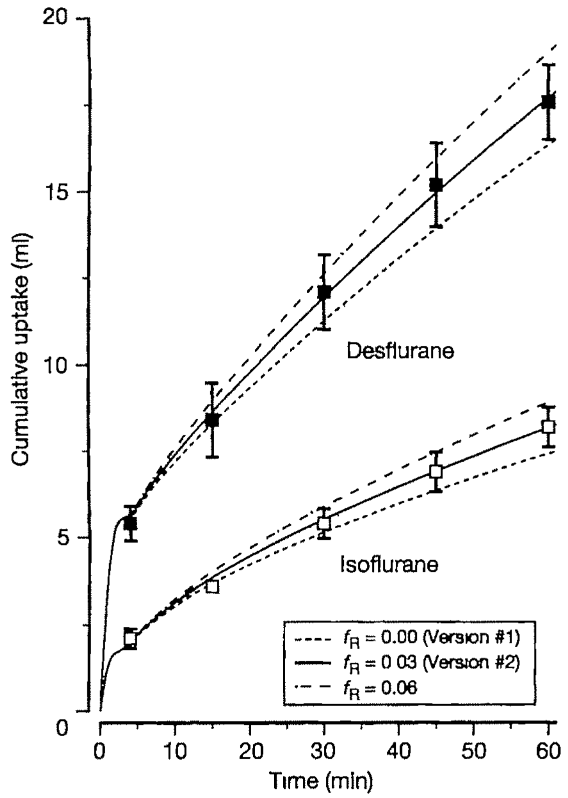

Fig 3 Cumulative uptakes of desflurane or isoflurane computed with three versions of the system model using different fractions of cardiac output redirected from the viscera to the adipose tissue: f_R=0.0 (version 1), 0.03 (version 2) and 0.06 The calculated uptakes are compared with those reported (a square with bars represents mean with 95% CI) by Hendrickx and co-workers.[12] They measured uptake of each anaesthetic, expressed in millilitres liquid, in 10 patients who received closed-circuit anaesthesia at 1.3 MAC with mechanical ventilation of the lungs The simulation is for their average 42-yr-old female patient of 1.65 m height, and 74 (desflurane) or 66 kg (isoflurane) body weight.

Table 5 Cardiac output partitioning in the two versions of the system model The blood flows through the compartments are expressed as fractions of cardiac output. Values for version 1 are data given by Lowe and Ernst.[30] In version 2, a fraction f_R of the cardiac output is redirected from the viscera to the adipose tissue (f_R=0.03, see text for calculation of the fractions for the individual tissue compartments) The liver compartment includes the liver itself and the whole portal system

	Compartment	Version 1	Version 2
Viscera	Kidneys	0.250	0.240
	Heart	0.050	0.048
	Brain	0.160	0.154
	Liver	0.300	0.288
Lean tissue	Muscles	0.130	0.130
	Connective tissue	0.060	0.060
Adipose tissue		0.050	0.080

values, but for nitrogen and carbon dioxide vol% has been used for the following reasons. Calculating the scaled differences for nitrogen would have led to dividing by zero. For carbon dioxide the differences found between calculated and measured values were relatively large; thus scaling would be less meaningful.

Table 6 shows that total error budgets for inspired concentrations are similar to those for end-expiratory concentrations. For desflurane, nitrous oxide, and oxygen, values of rmse are less than 12%. For carbon dioxide, there is an important total error budget of approximately 1.75 vol%. Performance measures are further reported only for end-expiratory concentrations, as their group rmse values tend to be slightly higher for most gases.

Version 1 vs 2

Each of the performance indicators was calculated four times, that is once for each version (1 or 2) and each stage (1 or 2). Results for biases for (end-expiratory) desflurane concentrations are summarized in Figure 4. For stage 1, all observations are nearly on the line of identity, indicating that the biases differ very little between versions. For stage 2, most observations are further from the line of identity and in the blank area, where the bias for version 2 is closer to zero. Regardless of version, the majority of observations suffer from under-prediction (negative bias) for stage 1 and over-prediction (positive bias) for stage 2 (Fig. 4).

Figure 5 displays the results for the biases for nitrous oxide and oxygen. All observations are not far from the line of identity. Differences between versions are less than 2.5% for most observations. Over-prediction predominates for nitrous oxide, but under-prediction for oxygen. Observations for nitrous oxide and oxygen are lying predominantly in blank areas, indicating that their biases for version 2 are closer to zero (Fig. 5).

Table 6 Overall predictive performance of both versions of the system model. Group rmses, [total error budgets (mean (SD))], are given per version for inspiratory and end-expiratory gas concentrations

	Unit	**Version 1**		**Version 2**	
		Inspired concentration	**End-expired concentration**	**Inspired concentration**	**End-expired concentration**
Desflurane	%	8.8 (4.5)	10.1 (5.0)	7.5 (3.6)	8.5 (3.7)
Nitrous oxide	%	9.3 (3.6)	9.4 (3.8)	8.0 (3.6)	7.8 (3.7)
Oxygen	%	8.9 (3.2)	11.7 (4.0)	7.6 (3.1)	10.0 (3.9)
Carbon dioxide	vol%		1.73 (0.57)		1.75 (0.58)
Nitrogen	vol%	0.89 (0.56)	1.10 (0.60)	0.81 (0.54)	0.97 (0.59)

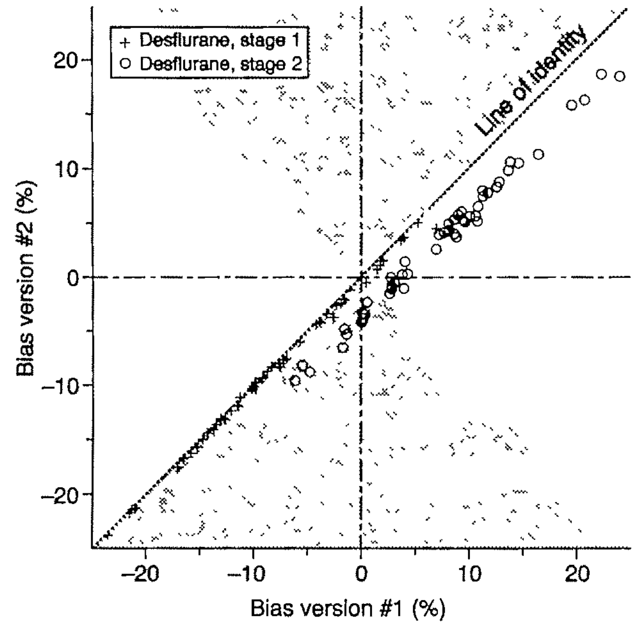

Fig 4 A scatterplot of the bias for version 2 *vs* the bias for version 1 obtained for end-expired desflurane concentrations. Each patient (*n*=50) is represented by one symbol per stage. One diagonal of the square is the line of identity, the other is the line where the biases have identical magnitudes but opposite signs. Observations in shaded areas are closer to zero bias for version 1, whereas observations in blank areas are closer to zero bias for version 2.

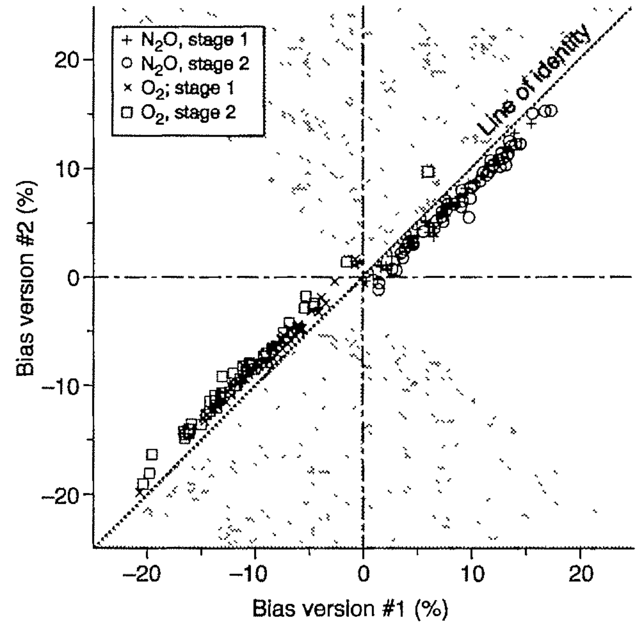

Fig 5 A scatterplot of the bias for version 2 *vs* the bias for version 1 obtained for end-expired nitrous oxide and oxygen concentrations. Each patient (*n*=50) is represented by four symbols, one per stage and per gas. One diagonal of the square is the line of identity, the other is the line where the biases have identical magnitudes but opposite signs. Observations in shaded areas are closer to zero bias for version 1, whereas observations in blank areas are closer to zero bias for version 2.

Table 7 outlines complete results, including statistical significances, for desflurane, nitrous oxide, and oxygen. For desflurane, results depend on stage. For stage 2, version 2 performs better than version 1 because rmse and bias are closer to zero. For nitrous oxide and oxygen, all performance variables are closer to zero for version 2, except for the scatters in stage 2.

For end-expiratory concentrations of carbon dioxide and nitrogen, rmse values were similar to those in Table 6, with biases of −1.1 to −0.7 vol% for nitrogen and 1.6 to 1.7 vol% for carbon dioxide.

Version 2: performance per stage and group

Each of the performance measures was calculated four times, that is once for each group (S or F) and stage (1 or 2). In Figure 6, each patient is represented by two symbols on each of the *x*–*y* plots, that is one symbol per stage. The iso-rmse semicircles allow a visual impression of the predictive performance of version 2.

The total error budget was generally greater for desflurane (Fig. 6A) than for nitrous oxide (Fig. 6B) and oxygen (Fig. 6C). Most observations for nitrous oxide are in the over-prediction zone, whereas most observations for oxygen suffer from under-prediction. The observations in Figure 6B and C stick to the *x*-axis, lying predominantly beneath the 5% scatter line. Thus, scatter made a much smaller contribution than bias to the error budget for nitrous oxide and oxygen.

Version 2: differences in performance between stages

Figure 6 and Table 8 show that notable differences between stages only exist for desflurane (plus signs *vs* circles; crosses *vs* squares). Figure 6A shows that only a minority of the observations (24%) for stage 1, but a majority (74%) for stage 2 is found in the semicircular area where rmse is less

Table 7 Predictive performance of version 1 *vs* version 2. Performance measures (mean (SD)) for end-expiratory gas concentrations are calculated per stage for both versions. The direction (sign) of the bias follows from its definition given in Table 1, that is predicted minus measured concentration. *$P<0.001$ version 2 *vs* version 1, for each stage

		Rmse (%)		**Bias (%)**		**Scatter (%)**	
		Version 1	**Version 2**	**Version 1**	**Version 2**	**Version 1**	**Version 2**
Desflurane	Stage 1	13.7 (5.3)	13.7 (5.4)	−8.8 (7.1)	−9.2 (7.0)	8.7 (3.6)	8.4 (3.5)*
	Stage 2	9.3 (5.7)	7.4 (4.2)*	7.2 (7.0)	3.2 (6.8)*	3.6 (1.9)	3.7 (2.0)
Nitrous oxide	Stage 1	7.1 (3.8)	5.8 (3.6)*	6.7 (3.8)	5.4 (3.7)*	1.9 (1.2)	1.7 (1.1)*
	Stage 2	9.6 (4.0)	7.9 (3.9)*	9.4 (4.0)	7.6 (4.1)*	1.6 (1.1)	1.7 (1.1)
Oxygen	Stage 1	9.1 (3.7)	7.7 (3.6)*	−8.8 (3.8)	−7.4 (3.9)*	1.6 (1.0)	1.5 (1.0)*
	Stage 2	12.1 (4.2)	10.3 (4.1)*	−11.7 (4.8)	−9.6 (5.1)*	1.6 (1.1)	1.8 (1.2)

than 10%. Most observations for stage 1 are in the under-prediction zone, whereas observations for stage 2 appear to be evenly dispersed either side of the +2% bias line (Fig. 6A).

The differences for desflurane are substantial in terms of bias (Table 8). In group S (n=36), mean bias in stage 1 is −10.1% *vs* +3.6% in stage 2. The magnitude of the difference between these sample mean biases is 13.7%, with a 99.9% confidence interval (CI) from 8.0 to 19.4%. In group F (n=14), this difference is 9.1%, with a 99.9% CI from 0.8 to 17.5 %.

Version 2: differences in performance between groups

The study failed to demonstrate differences in model performance between groups (Table 8).

Discussion

We quantified the predictive performance of our model[1 2] during desflurane anaesthesia using various regimens in settings of vaporizer and FGF. The principal findings were: (i) predictions largely agreed with clinical data; (ii) version 2 performed better than 1; (iii) clinically important differences between groups or between stages were not demonstrated, except for desflurane for which the model performed better during maintenance. Apart from the large discrepancy for carbon dioxide, most systematic errors were small, 2–10%.

Structure of the model

Despite these findings we cannot conclude that the complete structure of the model is correct. This is a general problem of complex physiological models.[14] Validating each and every variable in such a model may present insurmountable difficulties.[15]

The value for f_R in version 2 was found on the basis of data from an other institution [12] The results in Figure 3 lend credence to the broad validity of the model, but do *not* prove that version 2 is entirely correct. Our results even do not indicate that direct diffusion of desflurane from well-perfused organs into adjacent fat is an indispensable part of a physiological model. Nonetheless, large-scale diffusion between body compartments is a well-known physical process.[3 11 16–18] The over-prediction we reported earlier, especially during longer anaesthetics,[19] might have been minimized by adopting inter-tissue diffusion.

Diverting 3% of the cardiac output from viscera to fat (Table 5) represents inter-compartment diffusion only indirectly. Furthermore, an f_R in the range from 0.01 to 0.05 would also have been a legitimate choice as the uptake curves obtained with these values were within the 95% CIs shown in Figure 3.

Our results also do not prove that we are right in using a blood–gas partition coefficient for desflurane of 0.52.[10] This value is different from the most cited value[2] (0.42), but lies within the range of measured values. Even a value of 0.58 (SD 0.06) has been reported.[20] Illustrations of the impact of various values on desflurane wash-in and reasons for using 0.52 were given elsewhere.[2] It is noteworthy that our model uses the tissue–gas partition coefficients reported by Yasuda and co-workers.[9] Tissue–blood partition coefficients were obtained by dividing the latter coefficients by 0.52 (Table 5 in reference 1).

Accuracy for different gas species

There are some basic criteria to judge the accuracy of the model. First, valid models should not under-predict or over-predict reality in a systematic way. It is reasonable to expect a certain degree of bias for each patient. Nonetheless, the group bias should approximate zero. A value within ±10% can be defended as an acceptable approximation on the grounds that this is within the limits that can be achieved for control of concentrations clinically. Second, if the group bias approximates zero, the total error budget (rmse) should be acceptable for a majority (⩾90%) of the patients. A 0–10% group bias can indeed coexist with a significant dispersion of the individual results for bias and scatter. The accuracy of the model becomes unacceptable when the individual rmses are greater than can be reasonably expected on the basis of the biological variability found in a general human population. Although we arrived at defining objective criteria to determine whether a physiological model has 'acceptable' accuracy for the special case of closed-circuit anaesthesia,[19] further research is needed to define such rules for low-flow conditions, if at all possible.

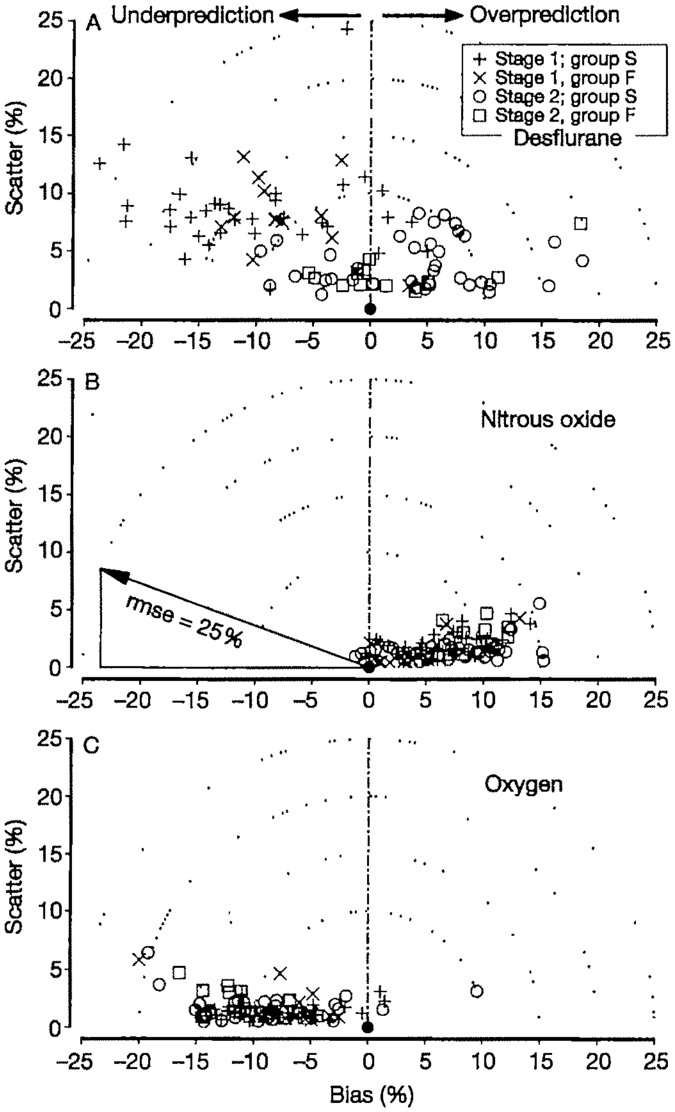

Fig 6 Predictive performance measures obtained with version 2 for end-expired desflurane, nitrous oxide and oxygen concentrations. The individual scatters of the 50 patients (36 in group S and 14 in group F) are plotted against their individual biases: Ideally, all observations for one gas would coincide with the black dot at (0,0) representing the point of ideal performance (rmse=0%). The semicircles are the iso-rmse lines from 10 to 25%. The distance between the black dot and a symbol is the rmse representing the total error budget for an individual. The mathematical relationship between rmse, bias, and scatter (Table 1) is visualized in the graph for nitrous oxide. This relationship is the same as that of the sides of a right-angled triangle If bias is the base of the triangle and scatter the perpendicular, then the rmse is the length of the hypotenuse.

For desflurane, nitrous oxide and oxygen, group biases are ≤10% (Tables 7 and 8). For desflurane, rmse values are less than 25% (stage 1) and less than 17% (stage 2) for ≥93% of the patients (Fig. 6). For nitrous oxide and oxygen, rmse values are less than 15% for 92–100% of the individuals.

The accurate performance of the model for nitrogen (rmse≈1 vol%) is not totally surprising. The largest stores of nitrogen are in the lungs and are washed out almost completely during the first minutes of an anaesthetic. The discrepancies between theory and experiment might have been greater during these very early stages, but they were omitted for reasons discussed further.

The mass balance model of Beams and co-workers[21]—based on the same specific breathing system—seems to represent clinical low-flow anaesthesia better than ours. In their study, however, actual patient exchanges for isoflurane, oxygen, nitrous oxide, and nitrogen were measured and used as input for the model. This points out that the predictive performance of a model heavily depends on variability in exchange rates of gases and vapours.

Can the cause of the systematic errors be elucidated?

In this study we could exclude errors induced by departures from the settings of the vaporizer as we measured the actual

Table 8 Predictive performance of version 2. Performance measures (mean (SD)) for end-expiratory gas concentrations are calculated per stage, in the S(low) group (n=36) and F(ast) group (n=14) The direction (sign) of the bias follows from its definition given in Table 1, predicted minus measured concentration *P<0.001 stage 1 *vs* stage 2, for each group. This study did not demonstrate differences between groups

		Rmse (%)		Bias (%)		Scatter (%)	
		Stage 1	**Stage 2**	**Stage 1**	**Stage 2**	**Stage 1**	**Stage 2**
Desflurane	Group S	14.7 (5.6)	8.1 (3.8)*	−10.1 (7.6)	3.6 (7.0)*	8.6 (3.6)	4.0 (2.1)*
	Group F	11.2 (4.1)	5.7 (4.7)	−7.0 (4.7)	2.1 (6.4)*	7.8 (3.3)	2.9 (1.5)*
Nitrous oxide	Group S	6.6 (3.4)	7.9 (4.2)	6.2 (3.5)	7.6 (4.5)	1.8 (1.0)	1.5 (0.9)
	Group F	3.9 (3.5)	8.0 (3.2)	3.4 (3.6)	7.7 (3.1)*	1.3 (1.3)	2.2 (1.3)
Oxygen	Group S	8.0 (3.2)	10.5 (4.2)*	−7.7 (3.8)	−9.7 (5.6)*	1.3 (0.6)	1.6 (1.1)
	Group F	6.9 (4.3)	9.7 (3.8)	−6.6 (4.1)	−9.5 (3.6)	1.8 (1.6)	2.1 (1.2)

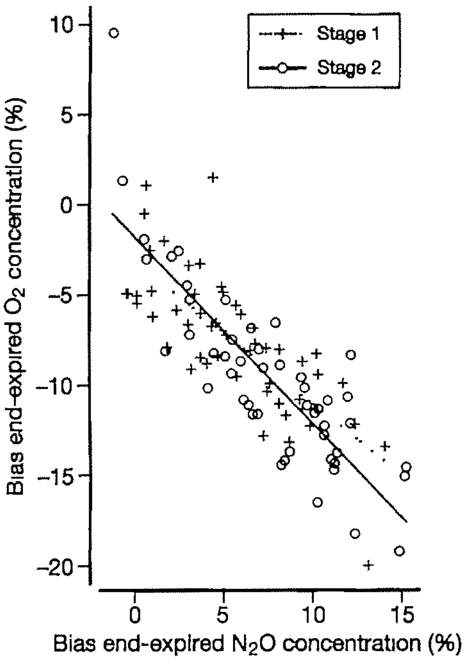

Fig 7 Scattergram showing relationship between the individual biases obtained with version 2 for the end-expired nitrous oxide and oxygen concentrations. There is one symbol per stage for each of the 50 patients. Note that one unit of bias has the same length on both axes. The regression lines have intercepts not far from zero and slopes not far from minus one.

delivered concentration at each setting. Although deviations between checks of the Rotameters cannot be excluded, it is very unlikely that temporary deviations would always occur in the same direction.

The under-prediction for oxygen could be simply explained by assuming that actual oxygen uptake was lower than predicted. This would conflict with prior notions that reported values were greater than those predicted by our model.[1] In addition, this single factor governed explanation might be too simplistic. There are many factors influencing the kinetics of the various gases, and their kinetics are interdependent.[2 22] This leads to propagation of errors and thus presents nearly insuperable difficulties in tracing the exact sources of error. As oxygen plus nitrous oxide make up about 90% of the gas mixture, it is almost certain that a negative bias in one will be associated with a positive bias in the other.

Assuming that the actual uptake of nitrous oxide was greater than that predicted would not only explain the over-prediction found for nitrous oxide, but also the under-prediction found for oxygen. Figure 7 confirms this by re-plotting data from Figure 6B and C to show a strong link between the individual biases for nitrous oxide and oxygen: r^2=0.58 and r^2=0.70 for stages 1 and 2, respectively. Others[23] also observed an actual uptake of nitrous oxide greater than predicted.

The complex array of sources for error is also not in favour of a simple explanation of the errors being less in stage 2 than in stage 1, but only for desflurane (Table 8). Under-prediction in stage 1 is no surprise as erroneous prediction of uptake of nitrous oxide may lead to erroneously predicted concentrations of oxygen (see above) and desflurane alike.[2] However, we also showed that certain combinations of cardiac output and ventilation present in a patient did not necessarily lead to grossly erroneous predictions for desflurane.[2] The actual value of each of the factors governing gaseous homeostasis in circle systems very likely differed from that assumed, but as a result of their complex interplay, systematic modelled-to-reality differentials in desflurane concentrations were absent during stage 2.

The systematic over-prediction for carbon dioxide (bias≈1.8 vol%) may be partially related to systematic measurement errors, despite the use of mass-charge ratio 12. Error-free assessment of relatively low carbon dioxide levels in gas mixtures containing high concentrations of nitrous oxide is a well-known problem in respiratory mass spectrometry. Carbon dioxide readings lower than expected have been reported.[24] We found that carbon dioxide levels, as measured by the mass spectrometer, were invariably lower than those assessed by the infrared analyser incorporated in the anaesthesia system, at least during controlled ventilation. It is puzzling, however, why calibration mixtures showed no error. Notably, two infrared analysers may differ up to 0.4 vol%.[25]

Research design

Early stages of the anaesthetic

A reservoir bag at the end of a 1-m length of corrugated tubing was used for spontaneous breathing and manual ventilation by mask with high flows of fresh gas. This was not mimicked in the simulation as the volume of tubing and bag (2 litres when full, but much <2 litres when squeezed) averaged over a respiratory cycle closely matches the volume of the standing bellows (1.5 litres when full). Future research might be improved by using the standing bellows for both spontaneous breathing and artificial ventilation of the lungs by mask—as advocated for two-handed mask ventilation of the difficult airway by a single individual.[26]

Early stages, such as pre-oxygenation and manual ventilation of the lungs, were omitted from calculations of performance measures because the values obtained for inspired and end-tidal concentrations were too inaccurate before intubation.

Nitrous oxide

As the present study may suffer from some error as a result of the use of nitrous oxide (as described above), further research would preferably also include a group of subjects breathing oxygen in air. This would allow studying the impact of nitrous oxide and (better) assessing the behaviour of nitrogen and carbon dioxide.

Alveolar ventilation

The value for arterial–end-expired $P\text{CO}_2$ difference, 0.533 kPa, was chosen to yield a 10% dilution factor for all patients. Others found a similar difference.[25 27] Future research will need to include the invasive sampling of arterial blood for blood–gas analysis if one would want to assess individual alveolar ventilation. This would help to investigate the sources for a bias for carbon dioxide.

Clinical implications

The target end-expired desflurane concentration was rapidly attained, that is within 6.1 min on average, with both FGF regimens. The average difference between the fast and slow scheme, 3.6 min, would probably be clinically unimportant in many cases (Table 4). The low solubility of desflurane thus allows the use of a low FGF even during induction.

Although our results are based on a limited array of FGF and anaesthetics lasting 1 h, we are confident that the model can be safely used to develop drug-dosing regimens for various purposes.[28] It is a unique feature of a physiological model to conceive such regimens for maintaining steady concentrations under different physiological conditions.[29] Obviously, model-based predictions must be validated and are *no* substitute for actual monitoring of gases and vapours.

Our results suggest that version 2 of the new system model is an adequate representation of desflurane anaesthesia in the clinical setting. It allows, with a known uncertainty, prediction of the behaviour of most gases present in the anaesthetic breathing system. Nonetheless, administration of inhalation anaesthesia based on this model must be guided by active monitoring.

Acknowledgement

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Predictive performance of a physiological model for enflurane closed-circuit anaesthesia: effects of continuous cardiac output measurements and age-related solubility data

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Background. The disposition of inhalation anaesthetics is governed by the factors described in the Fick principle.

Methods. We have recalibrated a previously validated physiological model for enflurane closed-circuit inhalation anaesthesia, using individual continuous cardiac output measurements as well as age-related enflurane solubility coefficients as inputs to the model. Two model versions using 'calculated' (Brody's formula) or 'measured' (thoracic electrical bioimpedance) cardiac output values, and two versions with 'standard' (fixed) or 'age-related' solubility coefficients were formulated.

Results. Data from 62 ophthalmic surgical patients were used to validate the predictive performance of the four model versions. The root mean squared errors (total error) and scatters (error variation) were similar with the extended model versions, but the group biases (systematic error component) were significantly less with the model versions that included age-related solubility compared with the versions using standard solubility coefficients (bias –0.76/–0.78% vs –3.44/–3.60%).

Conclusion. The inclusion of age-related solubility coefficients but not of continuous cardiac output measurements improves the predictive performance of the physiological model for closed-circuit inhalation anaesthetic conditions in routine clinical practice.

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Keywords: anaesthetics volatile, enflurane; equipment, breathing systems, closed-circuit; measurement techniques, mass spectrometry; heart, cardiac output; model, physiological; pharmacokinetics, uptake; pharmacokinetics, solubility

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The uptake and disposition of inhalation anaesthetic agents follows the Fick principle, and depends on the delivered anaesthetic concentration, on the patient's cardiac output as well as regional organ blood flow, and on blood and tissue solubility. To predict the end-expired anaesthetic concentrations following bolus injections of liquid enflurane, we previously validated a 14-compartment physiological model for closed-circuit inhalation anaesthesia.[1–3] This model, designated version C, incorporated a fixed estimate of the cardiac output calculated per patient (Brody's formula: cardiac output = (0.2 $kg^{0.75}$) litre min^{-1}), as well as anaesthetic solubility coefficients of a standard human.[4] Assuming a fixed value of the cardiac output during the entire course of anaesthesia is obviously an oversimplification and is inconsistent with the observations in clinical practice. In addition, Lerman and co-workers showed that the solubility of volatile anaesthetics varies with age.[5–7]

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We investigated whether the use of real-time continuously measured cardiac output values and age-related solubility coefficients, that is two variables from the Fick formula ($\text{Uptake}=dQ/dt\times\lambda\times(P_{in}-P_{out})$), would improve the prediction of end-expired anaesthetic concentrations in the clinical conditions of closed-circuit inhalation anaesthesia. Therefore, four extended versions of the physiological model were formulated: two model versions using calculated or measured cardiac output values (referred to as version C or version E, respectively, with standard solubility coefficients), and two corresponding versions with age-related solubility coefficients (referred to as version C' or E', respectively). The predictive performance of these various model versions was experimentally validated during routine clinical practice.

Methods

The structure of the model and modelling methodology has been described extensively elsewhere.[1–3] The model and methods are summarized here along with the modifications and additions necessary for this particular study.

Patients and anaesthetic procedure

After approval of the Institutional Ethical and Research Committee and informed consent, we studied 62 adult patients (ASA I or II) undergoing elective ophthalmic procedures. The patients were pre-medicated with diazepam (5–10 mg orally) and droperidol (2.5–5 mg orally) 1 h before surgery. Before induction of anaesthesia, pure oxygen was administered at a flow rate of 10 litre min^{-1} via a tight fitting mask for 3 min. Then anaesthesia was induced with fentanyl 0.1–0.2 mg i.v. and a dose of thiopentone sufficient to abolish the eyelash reflex, followed by vecuronium 0.1 mg kg^{-1} i.v. After spraying the vocal cords with 4.3% lignocaine, a cuffed tracheal tube was placed. The lungs of the patient were artificially ventilated with a high fresh gas flow of oxygen and nitrous oxide (1:2 ratio) for a maximum of 5 min or until the end-expired nitrogen concentration was less than 1 vol%. Next, the anaesthetic system was closed and closed-circuit anaesthesia started. The anaesthetic equipment was an Ohmeda Modulus CD anaesthesia system (Madison, WI, USA) with a standing bellows ventilator (Ohmeda 7850). The fresh gas flow of oxygen and nitrous oxide was adjusted manually to maintain the inspired oxygen concentration at 35–40 vol%. Tidal volume was adjusted to maintain the end-expired carbon dioxide concentration at 4.0–5.0 vol%. As the delivered tidal volume depends on the rate of fresh gas flow into the standing bellows ventilator, adapting the fresh gas flow to obtain the prescribed closed-circuit conditions necessitated frequent adjustments of the tidal volume and the gas flows at the start of closed-circuit anaesthesia.[8] Therefore, 5 min were allowed until we were confident that the tidal volume and gas flows were stable. Only data acquired after this initial non-steady state period were analysed.

Liquid enflurane was injected into the expiratory limb of the circuit: an initial volume of 0.02 ml kg^{-1} (loading dose) at the start of closed-circuit inhalation anaesthesia and repeated volumes of 0.01 ml kg^{-1} (maintenance doses) during anaesthesia. All anaesthetic procedures were performed by the same anaesthetist (P.M.V.). The time for start of ophthalmic surgery was within a maximum of 5 min after the start of enflurane administration. We did not use a rigid time schedule and did not aim to maintain a predetermined end-expired anaesthetic concentration, but modified the enflurane administration according to the patient's anaesthetic needs as in good clinical practice. Therefore, the non-invasive blood pressure, heart rate, heart rate variability (judged by ear with the aid of pulse oximetry), transcutaneous arterial oxygen saturation, and the end-expired enflurane concentrations (i.e. the best possible approach to the alveolar concentrations measured during routine circumstances), were carefully and continuously monitored.[9] If necessary in response to surgical stimuli, analgesia was supplemented with additional increments of fentanyl 0.05–0.1 mg i.v. A respiratory mass spectrometer (Centronic 200 MGA or QP9000; CaSE, Gillingham, UK) continuously sampled gas (40 ml min^{-1}) at the Y-piece of the anaesthetic circuit via a side-stream sampling port (the sample flow is part of the model). Before using the mass spectrometer we verified its calibration for enflurane with a certified calibration gas mixture (1% enflurane in 30% oxygen, 30% nitrous oxide and balance gas nitrogen; AGA Gas, Amsterdam, The Netherlands). The coefficient of variation of the mass spectrometer readings was 2%. The times and volumes of each liquid enflurane administration were noted.

Cardiac output was estimated and recorded continuously by a thoracic electrical bioimpedance monitor (BoMed NCCOM-3, software version 6; BoMed Medical Manufacturing Ltd Instruments, Irvine, CA, USA). This method gave the possibility of including direct non-invasive cardiac output measurements as a continuous non-linear and subject-specific input to the model. This device derives the cardiac output by measuring changes in electrical bioimpedance of the thorax.[10 11] Four pairs of surface electrodes were placed mid-circumferential on each side of the neck and on each side of the chest (equidistant from the xiphoid processus), and connected to the BoMed monitor. Cardiac output values were calculated and recorded from the average thoracic electrical bioimpedance for 12 successive acceptable heartbeats. The real-time cardiac output recordings, starting from immediately before the first injection of enflurane into the closed system, were processed in the appropriate model versions.

A personal computer with a 12-bit analogue-to-digital board (Keithley Metrabyte, Taunton, MA, USA) processed the signals from the mass spectrometer, the cardiac output monitor, and the anaesthesia system. On-line display of the respiratory waveforms allowed constant monitoring of the actual inspired and end-expired concentrations of nitrogen, oxygen, carbon dioxide, nitrous oxide, argon, and enflurane. The trends of the enflurane and oxygen concentrations in the last 20 min were also displayed continuously to provide a visual impression on the quality of the measurements. End-expired enflurane concentration and non-invasive cardiac output values were saved to disc every 10-s period for further off-line data processing.

Model and its versions

Initially a theoretical physiological 14-compartment model (the basic model version A), based on data from the literature for a standard human, was formulated to predict the end-expired concentrations of inhalation anaesthetics under closed-circuit conditions.[12 13] In the present study, four extended versions derived from the basic model were evaluated (Fig. 1). The formerly validated model version C uses a fixed, calculated cardiac output value. It was extended with real-time cardiac output measurements from each patient (version E). Versions C and E both used fixed solubility coefficients for a standard human, whereas two corresponding versions were created, versions C' and E' respectively, that incorporated age-related enflurane solubility coefficients (Table 1). For every patient each of the four model versions predicted the end-expired anaesthetic concentrations (i.e. four simulation runs per patient). After compiling the predicted and measured anaesthetic concentrations, the predictive performance measures were calculated by comparing the measured end-expired enflurane concentrations with those predicted by the four different model versions. The sequence of the data processing is depicted in Figure 2.

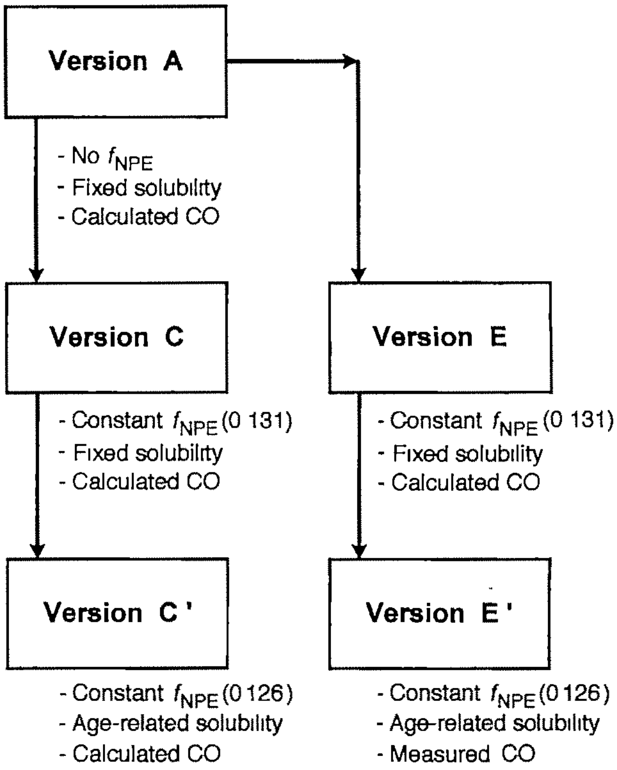

Fig 1 Four extended model versions of the basic physiological model (model version A) were formulated. The formerly validated version C uses a fixed value of the cardiac output calculated per patient (Brody's formula Q=0.2 BW$^{0.75}$).[1–3] In the present study the model version E, which uses the continuous cardiac output measurements tracked from the individual, was validated. Both versions C and E use the fixed solubility coefficients of a standard human.[4] To evaluate the influence of the factor solubility, two extended versions (C' and E') which adopt age-related partition coefficients according to the studies of Lerman and Malviya (Table 1) were also tested.[5–7] The four model versions tested all account for a constant fraction of non-pulmonary elimination (f_{NPE}) for enflurane. The small difference between the f_{NPE} for the versions C/E *vs* C'/E' (that is 0.131 *vs* 0.126) was effected by the different solubility data (fixed *vs* age-related) used while determining the appropriate size of non-pulmonary elimination for enflurane (the procedure was described in a previous study).[1]

Table 1 Enflurane solubility coefficients *According to Lowe and Ernst.[4] **According to Lerman and co-workers[5 6] and Malviya and Lerman,[7] in the present study we had to interpolate for the intervening ages of the individual patients as Lerman and co-workers reported values for only five different ages. Where no age-adjusted values were available, the data reported by Lowe and Ernst were used. (The studies were reported without reference to gender)

	Version C/E* (all ages)	VersionC'/E'** 0 yr	5 yr	35 yr	60 yr	80 yr
Blood/gas	1.9	1.78	1.78	2.07	1.91	1.79
Tissue/blood						
Lung tissue	1.3					
Kidney	1.2					
Heart	1.6	1.23		1.15	1.49	1.35
Brain	1.6	0.92		1.30	1.28	1.37
Liver	2.0	1.48		1.45	1.71	1.89
Muscle	1.6	0.81		1.09	1.60	2.22
Connective tissue	1.4					
Adipose tissue	37.0			40.97	45.57	43.48

Predictive performance measures and statistics

The following measures were used to determine the predictive performance of each model version (Table 2). The prediction error (*pe*) is the difference between the predicted and measured concentration, expressed as a percentage of the measured value. The *pe* and squared prediction error (pe^2), calculated for each 10-s period, were used to provide three additional predictive performance measures. (1) The mean squared error (*mse*) is the average of the squared prediction errors per patient. The root-mean squared error (*rmse*) is a measure of the total error budget for an individual patient during one anaesthetic procedure: it is not influenced by the sign of the prediction errors and can be decomposed into two terms: bias and scatter. (2) The bias is the average of the prediction errors for an individual patient: it is a measure of the systematic error component and can be either positive or negative, indicating either over- or under-prediction. (3) The scatter is a measure of the variation of the prediction errors around their mean (bias) during one anaesthetic procedure. Finally, calculating the average of all the individual *rmses*, biases or scatters—one per patient—yields the group *rmse*, the group bias or the group scatter.

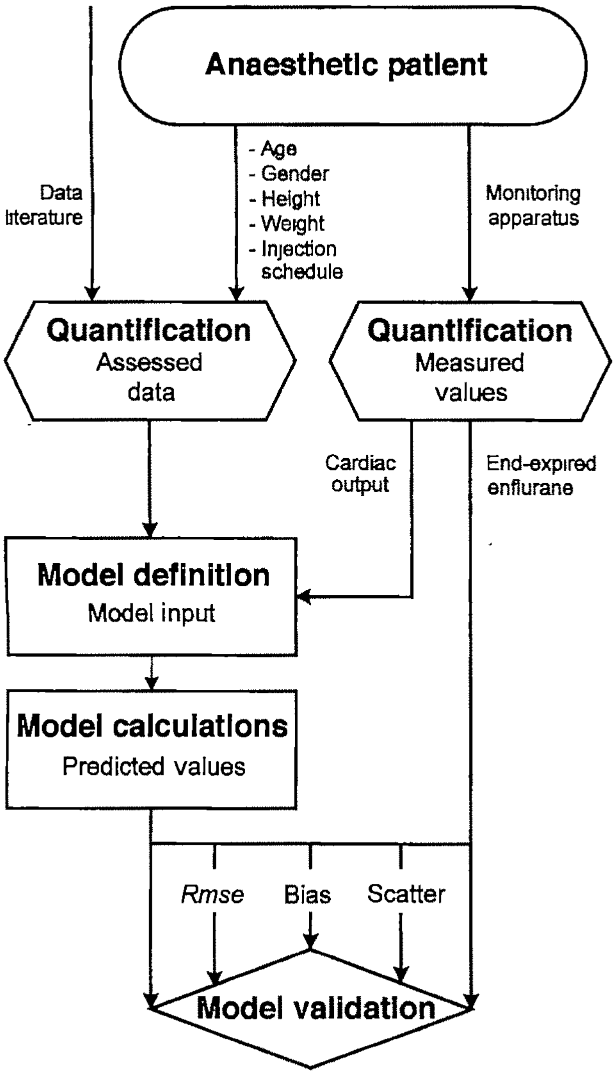

Fig 2 For the data processing, the patient characteristics (age, gender, body weight, and height) were collected for each patient The enflurane administration schedule (injection time and volume) was added as input to the model. The amount of liquid enflurane per injection was converted into millilitres of vapour, and supplied to the model as if added to the anaesthetic system over a 60-s interval (i.e the average evaporation time) The continuous cardiac output measurements per patient were entered to the model as an independent variable. Next, the appropriate version of the model was selected and activated to generate the predicted time courses of the end-expired enflurane concentrations by running a special purpose simulation programme (TUTSIM®, Meerman Automation, Neede, The Netherlands)[12] For each patient and anaesthetic procedure the end-expired concentrations were predicted by applying the appropriate version of the model. Finally the model's predictive performance measures were calculated by comparing the predicted with the measured end-expired enflurane concentrations quantitatively.

Friedman's analysis of variance was used to analyse the differences in the predictive performance measures across the four model versions. If the Friedman analysis revealed a difference for a particular performance measure, post hoc analysis using sign tests for paired data were done to further evaluate the differences between the model versions.[14] Differences yielding $P<0.05$ were considered significant.

Results

The characteristics of the 62 adult patients (45 males) are listed in Table 3. Details of the closed-circuit conditions (Table 4) show that a total of 438 ml of liquid enflurane (450 injections) was used to provide more than 63 h of anaesthesia, during which 23 000 values of end-expired enflurane concentrations were recorded. Figure 3 shows the average values of the measured and calculated cardiac output data per patient. Although the group means of the

Table 2 Predictive performance measures (*pe* is the prediction error in per cent, *n* is the number of measurements per patient, pe_i is the *i*-th prediction error and *me* is the mean prediction error, $C_{A,p}$ and $C_{A,m}$ are the predicted and the measured alveolar concentrations of enflurane)

$pe = \dfrac{C_{A,p} - C_{A,m}}{C_{A,m}} \times 100$	= Prediction error, per pair of predicted and measured values
$\sqrt{\dfrac{1}{n}\sum_{i=1}^{n} pe_i^2}$	= *Rmse* = √(Bias² + Scatter²), total error budget
$me = \dfrac{1}{n}\sum_{i=1}^{n} pe_i$	= Bias, systematic component of the error
$\sqrt{\dfrac{1}{n}\sum_{i=1}^{n}(pe_i - me)^2}$	= Scatter, dispersion of the errors (*pe*) around their mean (*me*)

measured (5.28 (SD 1.25) litre min^{-1}) and the calculated (5.17 (0.66) litre min^{-1}) cardiac output values were very similar, the range was more dispersed for the measured (2.91–8.03 litre min^{-1}) compared with the calculated (3.76–6.65 litre min^{-1}) cardiac output data. The trend of the measured cardiac output values throughout the anaesthetic procedures can be appreciated from Figure 4.

The results of the three predictive performance measures (the group *rmse*, bias and scatter) for the four model versions are summarized in Table 5. There were no statistically significant differences across the four group *rmses*. The total error budget (*rmse*) was mainly the result of variations of the prediction errors around their mean (the scatter) rather than the result of the systematic error component (the bias). There was a statistically significant difference across the group biases of the four versions ($P<0.0001$). This difference is mainly determined by the differences between the model versions that implemented age-related solubility coefficients (C' and E') *vs* the versions that used standard solubility coefficients (C and E). However, there was no significant difference for the biases of the versions that used calculated cardiac output values (C and C') *vs* the versions that used measured cardiac output data (E and E'). The rank order for the magnitude of the group biases was E>C>E'≥C'. Similar results were found for the group scatters: the age-related versions (C' and E') performed significantly though only slightly better (i.e. a statistically smaller scatter) compared with their non-age-related counterparts (C and E).

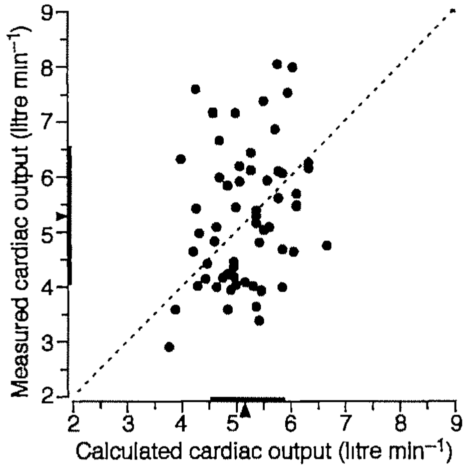

Fig 3 Scattergram of the cardiac output values· that is the calculated *vs* the mean measured cardiac output (l min^{-1}) per patient The triangles and thick lines on the abscissas and ordinates, represent the group mean cardiac output and SD, respectively The coefficient of variation was 13% for the calculated *vs* 24% for the measured cardiac output value. Both methods correlate moderately well (R^2=0.064).

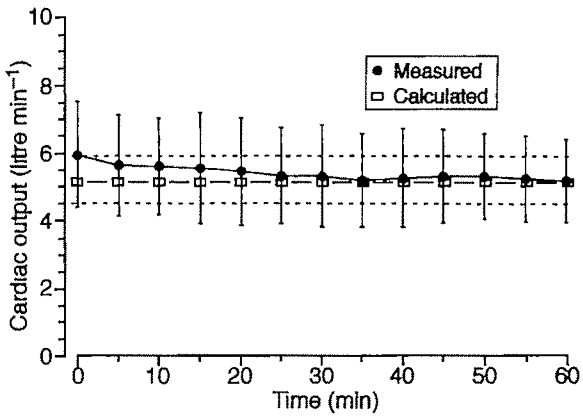

Fig 4 The group means cardiac output values (litre min^{-1}) are plotted over time (in blocks of 5 min). The mean calculated (□, SD dotted line) values of the cardiac output prove to be a good average of the mean measured (●, SD bars) cardiac output values throughout the different stages of routine surgical anaesthesia.

Table 3 Anthropometric patient characteristics (n=62)

Characteristic	Mean (SD)	Range
Age (yr)	43.1 (15.7)	18–73
Weight (kg)	76.7 (12 9)	50–107
Height (m)	1.76 (0 08)	1.56–1 96
Body mass index (kg m^{-2})	24 7 (3.4)	18 4–33 8
Body surface area (m^2)	1.93 (0 18)	1 53–2 33

Table 4 Details of the closed-circuit conditions (n=62)

	Mean (SD)	Range
Duration (min)	61 7 (17.6)	35–131
Number of data points	371 0 (105 5)	211–787
Number of injections	7 3 (1 6)	4–12
Injections per hour	7.2 (1.0)	5.2–9 8
Volume of liquid enflurane (ml)	7.1 (1.6)	4 2–12.0
Volume of liquid enflurane per hour (ml)	7 1 (1.3)	4.1–9 8
End-expired enflurane measured (vol%)	0.93 (0 19)	0.56–1.32

Table 5 Predictive performance measures of the different model versions (mean (SD)). *Friedman two-way analysis of variance; †statistically significant different *vs* non-accent counterparts (sign test for paired data), ‡statistically significant different *vs* version C (sign test for paired data)

	Version C	Version C'	Version E	Version E'	P-value*
Rmse (%)	18 70 (6 86)	18.77 (6 94)	19.14 (7 81)	18 79 (8 07)	<0 67
Bias (%)	–3 44 (15 77)	–0 76† (16 61)	–3 60 (17 13)	–0 78† (17.49)	<0 0001
Scatter (%)	11.32 (3 38)	10 84† (3 24)	10.74 (3 10)	10 31† ‡(3.03)	<0 0001

Discussion

In this study, we assessed the effect of a further individualization and subject-specific stratification of the model input by identifying and using individual patient factors given in the Fick formula. The predictive performance of a physiological model for closed-circuit anaesthesia is improved by incorporating age-related solubility coefficients instead of the solubility coefficients reported for a standard human. In contrast, model-based predictions of end-expired enflurane concentrations were not better if fixed calculated cardiac output value was replaced with continuous measured cardiac output data. Our results suggest that version C' (using a fixed cardiac output and age-related solubility data) is the most appropriate model to predict the end-expired anaesthetic concentration of enflurane during closed-circuit anaesthesia, while aiming at a constant level of the end-expired anaesthetic concentration and using the bolus injection technique in a routine clinical setting.

Cardiac output

Measured cardiac output values did not improve predictions, but some aspects need to be discussed. Brody's equation is used for a standard human under basic, resting conditions and is derived from a large 'normal' sample population. It does not necessarily predict an output for the individual patient (e.g. during surgery) and might under- or over-predict the measured cardiac output values in the clinical situation. A more reliable approach for dealing with variability is to gain subject-specific knowledge through the incorporation of individual measurements. In this study, electrical bioimpedance monitoring provided us with a simple continuous non-invasive measurement of cardiac output.[11]

Our patients underwent routine ophthalmic procedures and this type of surgery is usually not associated with large haemodynamic alterations. Because cardiac output remained stable we cannot be sure that extreme changes in cardiac output, for example during major surgical procedures, might influence the model predictions. In many models of inhalation anaesthesia, cardiac output should theoretically influence the disposition of inhalation anaesthetics. Nonetheless, in the absence of actual data, most authors had to build their models using approximate estimates for a standard human because more detailed information was not available.[15–17] Lockwood and co-workers performed computer simulations and argued that the initial uptake of volatile anaesthetics in closed-system anaesthesia, with a steady end-expired anaesthetic concentration, would not be affected by changes in cardiac output.[18] Several mechanisms could compensate for changes in uptake caused by changes in cardiac output. Using a continuous infusion of enflurane in a closed breathing system during cardiac bypass surgery, the same research group did not find a quantitative relationship between anaesthetic uptake and cardiac output.[19] Hendrickx and co-workers showed that cardiac output had no major impact on the prediction of sevoflurane kinetics during feedback-controlled closed-circuit conditions.[20 21] Our experimental findings confirm the theoretical calculations of Lockwood and Lerou and co-workers, and suggest that earlier work overestimated the importance of cardiac output for the predictive performance of models concerning closed-circuit inhalation anaesthesia.[18 22]

Theoretically, oscillations in the enflurane concentrations caused by the intermittent bolus injection technique might cause changes in cardiac output and we were interested whether this would influence the quality of the model predictions. We found no effect of injections on continuous cardiac output measurements, and confirm the findings of a recent study by Couto da Silva and co-workers who noted no major fluctuations on the systolic arterial pressure when using the intermittent bolus injection technique during closed-circuit anaesthesia.[23] Injection into the expiratory limb allows dilution in the ventilatory circuit and this attenuates the peak effects of the bolus injection technique. Also, the myocardium is saturated by more than 95% after three time constants, that is within only 10 min, so the peak loads of the anaesthetic injection method would not cause detectable variations of cardiac output.

The haemodynamic effects of inhalation anaesthetics are profoundly influenced by individual variability, and changes in cardiac output (body perfusion) do not cause proportional changes in blood flows to the different compartments (tissue perfusion).[24] Both Ashman and Cowles suggested that the construction of realistic models would need the inclusion of more detailed circulatory effects of anaesthesia, but they also recognized that the fractional flow and blood volume of each organ or compartment is difficult to measure in humans.[25–27] They stated that the changes in cardiac output and its distribution influence the size of all compartments, and the assumption that the partitioning of cardiac output does not change clearly also is an oversimplification. As measurement of regional organ blood flow in humans is not feasible during routine surgery, inclusion of continuously measured rather than fixed relative organ flows in physiological models seems unwarranted at present.

Solubility

Tissue and blood solubility coefficients are important in the prediction of the kinetics of inhalation anaesthetics during closed-circuit anaesthesia. The tissue/gas solubility coefficients reported by early investigators showed large differences (>150%) and also the ranges reported in single studies may be very large. The older 'standard' coefficients were about 30% higher than the values determined more recently.[4 6 28–30] Table 1 shows that the age-related enflurane solubility coefficients for the compartments of the vessel rich group (especially brain, heart and liver) are considerably less than the older fixed solubility coefficients.

Body composition changes with age and this will influence the pharmacological behaviour of inhalation anaesthetic agents. In the prediction of the pharmacokinetics of inhaled anaesthetics, solubility coefficients are particularly important during the first hour of anaesthesia. The model versions that used standard coefficients gave a small but systematic under-prediction, which could be corrected by the implementation of age-related solubility coefficients, suggesting that the age-related coefficients are better than the older standard coefficients.

The solubility of anaesthetic agents may vary between patients and between tissues. Solubility is also influenced by changes in body temperature, blood and tissue composition, genetic predisposition, and other unknown physiological influences.[28] Even during the course of an anaesthetic, there may be rapid changes of the anaesthetic solubility caused by acute changes in blood (and tissue) composition. Steady-state clinical conditions suitable for accurate determinations of the anaesthetic solubility are often impossible to achieve *in vivo*.[31 32] So, solubility data must be interpreted cautiously in the clinical setting. In addition, the present model does not account for a possible redistribution of anaesthetics within or from one tissue to another (inter-compartmental diffusion).

We found that this physiological 14-compartment model is robust, as the group-bias remained below 10% and the *rmse* was less than 30% for most (>90%) of the patients. These criteria were used in earlier validation studies for the model, as this does not result in systematic over- or under-prediction (bias) and 30% is a limit imposed by the biological variability.[2] The true picture will be complex because detailed information on the cascade of kinetics of the volatile anaesthetics is not well known.[21 33] During daily anaesthetic practice, fast and accurate gas monitoring systems are available, and anaesthetic equipment may now have adequate feedback control for anaesthetic agent delivery. This reduces the importance of on-line kinetic models for the routine clinical administration of inhalation anaesthesia. However, physiological models remain important to allow a more fundamental understanding of the process of inhalation anaesthesia, and can be valuable teaching tools when used in patient simulators.[17] These models should be updated regularly with recent data obtained in new research and the performance of the models should be explored in real clinical circumstances.

In conclusion, we studied the effect of two factors that control anaesthetic uptake according to the Fick principle, continuous cardiac output measurements and age-related solubility coefficients, on the predictive performance of a physiological model for closed-circuit enflurane anaesthesia. Cardiac output measurements did not improve the model predictions, but recalibration with age-related solubility coefficients improved the predictive performance of the model.

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Fresh gas flow is not the only determinant of volatile agent consumption: a multi-centre study of low-flow anaesthesia[†]

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Methods. Seven academic centres studied 302 patients, using desflurane, enflurane, halothane, or isoflurane using circle-systems and Dräger Julian anaesthetic machines, with fresh gas flows ($\dot{V}_F$) of 3, 1, and 0.5 litre min^{-1}. Volatile agent partial pressures in the breathing system were recorded and agent consumptions measured by weighing.

Results. At these flows, desflurane consumption depended on $\dot{V}_F$. In contrast, halothane consumption was not influenced by $\dot{V}_F$. Isoflurane and enflurane showed differences in consumption between flows of 0.5 and 3 litre min^{-1}. Stepwise linear regression suggested that besides $\dot{V}_F$, other factors influenced consumption of the more soluble agents (sex, age, weight, height, altitude, and temperature). The partial pressure ratios were independent of $\dot{V}_F$ for desflurane (end-tidal to fresh gas=0.8), but the ratios of the more soluble agents varied with $\dot{V}_F$ (end-tidal to fresh gas=0.3–0.7).

Conclusions. At $\dot{V}_F$ that involves significant re-breathing, consumption of soluble agents depends only partially on $\dot{V}_F$. These results can be explained using Mapleson's hydraulic analogue model.

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Keywords: anaesthesia, audit; anaesthetics, volatile; equipment, anaesthesia machines

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The rising costs of inhaled anaesthetic drugs, and especially the newly introduced agents, sevoflurane and desflurane, have influenced increasing numbers of anaesthesiologists to use decreased fresh gas flows ($\dot{V}_F$) in circle-absorber breathing systems. Studies of the economics of anaesthesia have used mathematical models to predict anaesthetic consumption,[1–3] and it is generally accepted that lower $\dot{V}_F$ allow less consumption of anaesthetic agent.[4–7] While this principle cannot be refuted when comparing high $\dot{V}_F$ with low $\dot{V}_F$, few studies have determined how much anaesthetic is saved by using low $\dot{V}_F$ in comparison to moderate $\dot{V}_F$ in clinical practice.[7 8]

The purposes of this study were: (i) to determine consumption of volatile anaesthetic agent using circle-absorber systems at moderate, low and minimal $\dot{V}_F$ (for the purpose of this study moderate fresh gas flow is defined as a flow of 3 litre min^{-1}; low fresh gas flow 1.0 litre min^{-1} and minimal fresh gas flow 0.5 litre min^{-1}). (ii) To evaluate the differences between vaporizer settings and end-tidal agent partial pressures that are achieved at these flows. Clinicians administered the anaesthetics as they would have done in clinical practice, according to their judgement of patient requirements.

Methods

The study was a multi-centre trial at all seven university Faculties of Medicine in South Africa. Studies used standard anaesthetic machines equipped with carbon dioxide absorber circle breathing systems and vaporizers outside the circuit (Drager, model 'Julian', Dragerwerk, Lübeck, Germany). Written informed consent was obtained from 302 adult patients aged 18–65 yr, of ASA I or II status, who were to undergo surgery. Using tables of random numbers, patients were allocated to one of four groups who received halothane or enflurane or isoflurane or desflurane. Each group was randomly subdivided into three subgroups who

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Table 1 Initial settings for fresh gas flow and vaporizers after tracheal intubation These settings served as an initial guide and could be changed as determined by patient response

Initial phase (first 10 min)	Nitrous oxide:oxygen (litre min^{-1})	3:1.5		
		Vaporizer settings (kPa)		
	Halothane	1.0–1.5		
	Isoflurane	1.0–1.5		
	Desflurane	3.8–4.0		
	Enflurane	2.0–2.5		
Flow reduction (maintenance of anaesthesia)		Moderate flow (3 litre min^{-1})	Low flow (1.0 litre min^{-1})	Minimal flow (0.5 litre min^{-1})
	Nitrous oxide:oxygen (litre min^{-1})	2:1	0.5:0.5	0.2:0.3 >80 kg, 0.2:0.4
	Halothane (kPa)	1.0–1.5	2.0	2.5–3.0
	Isoflurane (kPa)	1.0–1.5	2.0	2.5
	Desflurane (kPa)	3.8	3.8–4.0	3.8–4.0
	Enflurane (kPa)	1.2	3.0	3.5

received one of the following $\dot{V}_F$ during maintenance of anaesthesia (litre min^{-1}): 3, 1, or 0.5. There were, therefore, a total of 12 groups. Exclusion criteria included significant cardiac, pulmonary, renal, or neurolgical disease, pregnancy, previous adverse response to inhaled agents, patients undergoing regional or total i.v. anaesthesia, surgery with special requirements (e.g. cardiothoracic, neurosurgical), and procedures with an expected duration of less than 30 min.

No pre-medication was given. Monitoring provided by the Julian anaesthetic machine included ECG, pulse oximetry, nasopharyngeal temperature, non-invasive arterial pressure, capnography, inspired and expired gas partial pressure measurement (oxygen, nitrous oxide, volatile agent), airway pressure, tidal volume, ventilatory frequency, and minute volume. Neuromuscular transmission was monitored by train-of-four nerve stimulation.

After pre-oxygenation with 100% oxygen ($\dot{V}_F$ 6 litre min^{-1}) and establishing an i.v. infusion using local anaesthesia, fentanyl 3.0 μg kg^{-1} was administered intravenously to suppress the response to tracheal intubation. Induction of anaesthesia was with thiopentone 3–5 mg kg^{-1} and vecuronium 0.08 mg kg^{-1} followed by manually controlled ventilation by mask with V_F settings of nitrous oxide:oxygen (3.0:1.5). Anaesthetic vapour was introduced after tracheal intubation using Table 1 as an initial guide to the dosage that could be adjusted according to patient response. These initial vaporizer settings were based upon the following calculation: $F\text{E}_{AN} = (1.3 - F\text{E}_{N_2O}) \times \text{MAC}$, where $F\text{E}_{AN}$ = fractional expired partial pressure of the volatile agent in question, $F\text{E}_{N_2O}$ = fractional expired concentration of nitrous oxide (1.3 × MAC was assumed to be the volatile agent expired partial pressure sufficient to suppress movement on skin incision in 95% of patients.[9–11] For a partial pressure of 66 kPa for nitrous oxide these initially targeted expired partial pressures (kPa) were: halothane 0.5, isoflurane 0.74, desflurane 3.8, enflurane 1.2.

This initial wash-in period lasted 10 min to allow for initial rapid uptake of nitrous oxide and elimination of nitrogen, after which $\dot{V}_F$ was reduced with initial vaporizer and nitrous oxide:oxygen settings as shown in Table 1. If the inspired partial oxygen partial pressures decreased to less than 30 kPa during maintenance of anaesthesia, changes were allowed by increasing the oxygen $\dot{V}_F$ and simultaneously reducing the nitrous oxide $\dot{V}_F$ as follows: during low flow (1 litre min^{-1}) by 50 ml min^{-1} for each gas and during minimal flow (0.5 litre min^{-1}) by 100 ml min^{-1} for each gas.

If depth of anaesthesia had to be changed, the following procedures were followed. If a rapid change was not required, the vaporizer setting was adjusted while maintaining the $\dot{V}_F$. To increase inspired partial pressure, 'overpressure' was used if deemed necessary and to decrease inspired partial pressure, the vaporizer was temporarily shut off as needed. If a rapid change was required, the V_F was increased to 3 litre min^{-1} in addition to adjusting the vaporizer setting. During low and minimal $\dot{V}_F$ the vaporizer was shut off towards the end of the procedure (15–20 min) to allow the inhaled vapour partial pressure to decrease slowly. Additional neuromuscular blocking agent was administered as necessary.

Residual neuromuscular block was antagonized at the start of skin closure using neostigmine (0.04 mg kg^{-1}) mixed with glycopyrrolate (0.006 mg kg^{-1}). The vaporizer and nitrous oxide supply was shut off and the V_F increased to 6 litre min^{-1} of oxygen after the last skin stitch had been applied. The ventilatory frequency was reduced to allow the $P\text{E}'_{CO_2}$ to increase to a maximum of 6.5 kPa to initiate breathing.

The following were automatically recorded to computer disk at 5-s intervals, from the time that pre-oxygenation began until the patient awoke:

- Fresh gas flow
- Oxygen concentration in the fresh gas
- Inspired and end-tidal partial pressures of: volatile agent, nitrous oxide, oxygen, carbon dioxide
- Tidal volume, ventilatory frequency
- Oxygen saturation (pulse oximetry)
- Heart rate (from the pulse oximeter)
- Non-invasive arterial pressure (mean) measurements
- Nasopharyngeal temperature

Table 2 Details of the 302 patients studied, grouped according to fresh gas flow and drug administered Results are presented as mean (SD). n=number of patients in the group, $\dot{V}_F$=fresh gas flow; BMI=body mass index; duration=duration of volatile agent administration

Agent	$\dot{V}_F$ (litre min^{-1})	Age (yr)	Height (cm)	Weight (kg)	BMI	Duration (min)	Sex		ASA status			Altitude	
							Male	Female	I	II	III	Sea	>1300 m
Desflurane	0.5, n=26	38 7 (12.7)	163.9 (8.7)	66 1 (10.8)	24.8 (4.9)	109.6 (72.5)	7	18	21	25	0	13	13
	1, n=26	41.4 (13 9)	161 8 (6.5)	66 5 (14.7)	25.4 (5.2)	97.9 (86 2)	5	21	18	7	1	12	14
	3, n=24	40 4 (10 4)	165 0 (10 6)	76.3 (16.7)	28.3 (7 0)	80.8 (48 2)	5	19	15	8	0	12	12
Enflurane	0.5, n=23	41 3 (13 2)	163 5 (9 1)	70 7 (14 3)	26.5 (5.3)	80 4 (40 3)	4	18	16	5	1	12	11
	1, n=25	35.7 (11.8)	163.4 (9 0)	67 1 (15.3)	25 5 (5.9)	96.3 (69 6)	8	17	19	5	1	12	13
	3, n=24	41 3 (14.3)	162 7 (8.6)	67.3 (12.3)	25 7 (5 9)	101.1 (67.2)	6	18	18	6	0	13	11
Halothane	0.5, n=25	42 2 (10 0)	165 30 (8 2)	71 7 (14 7)	26.3 (5.2)	91 4 (40 7)	7	18	16	8	0	12	13
	1, n=27	41 0 (11.1)	168.6 (15 4)	68.8 (17.9)	24.4 (4.6)	88.30 (64 6)	11	16	17	8	2	13	14
	3, n=24	38 7 (11 1)	164 0 (12 2)	73 6 (14 6)	28 0 (6.4)	85.5 (42.7)	6	16	15	9	0	12	12
Isoflurane	0.5, n=26	37 4 (11 9)	166.1 (6.7)	67 1 (13 9)	24 1 (5.5)	81 7 (64 8)	11	14	19	6	0	14	12
	1, n=25	41 3 (9.5)	166.3 (9.5)	68.8 (13.0)	24.6 (4.7)	62.0 (35 0)	6	19	16	9	0	12	13
	3, n=26	41 6 (10.9)	168 5 (9.6)	72 3 (13.3)	25.9 (5 6)	95.3 (58 1)	7	18	16	10	0	14	12

Table 3 Summary of statistical differences (P<0.05) in agent consumption and partial pressure ratios between the three fresh gas flow groups V_F=fresh gas flow Ratios of volatile agent partial pressures during maintenance of anaesthesia F_A/F_I=end-tidal to inspired; F_I/F_D=inspired to fresh gas flow; F_A/F_D=end-tidal to fresh gas flow. Numbers refer to fresh gas flow groups 0 5, 1.0, and 3 litre min^{-1}

	Rate of consumption		F_A/F_D and F_I/F_D		F_A/F_I	
	Significant difference P<0.05	No difference	Significant difference P<0.05	No difference	Significant difference P<0.05	No difference
Desflurane	All three V_F			All three V_F		All three V_F
Enflurane	0 5 and 3	0.5 and 1, 1 and 3	All three V_F		0 5 and 1	0 5 and 3, 1 and 3
Halothane		All three V_F	All three V_F		1 and 3	0.5 and 1, 0.5 and 3
Isoflurane	0.5 and 3	0 5 and 1, 1 and 3	All three V_F			All three V_F

Times of adjustments to $\dot{V}_F$ and vaporizer settings were recorded manually.

After completion of the procedure the mass (g) of volatile agent was measured using mass balances capable of measuring to 0.1 g.*

Calculations

The data were imported to a computer spreadsheet (Microsoft Excel 97) for analysis. For each patient the arithmetic mean of the end-tidal anaesthetic partial pressures that had been recorded every 5 s were calculated for the duration of volatile agent administration (MF_A). The following anaesthetic agent partial pressure ratios were calculated and plotted at 5 s intervals: end-tidal to inspired (F_A/F_I); inspired to fresh gas (F_I/F_D); end-tidal to fresh gas (F_A/F_D). These ratios were noted at the following times: at the end of the 10-min wash-in period and at a later time during anaesthetic maintenance when these ratios were not changing (i.e. at 'steady state'). Mean rate of anaesthetic agent consumption was calculated by dividing the total mass used by the time that the anaesthetic vaporizer was switched on.

Data analysis

Statistical analysis was done with Statistical Analysis Support System (SAS), Version 6 Release 12, SAS Institute Inc., BMDP Statistical Software Inc. As the data were not always normally distributed, non-parametric, distribution-free tests were performed. Comparisons between two groups were done using the Mann–Whitney test or where appropriate, the Wilcoxon signed ranks paired test. Multiple group comparisons were done using Kruskal–Wallis one-way analysis of variance followed by post hoc multiple comparisons (Tukey's test). An alpha-value of 0.05 or less was regarded as indicating statistical significance.

To identify factors that influenced rate of consumption of anaesthetic agent, stepwise multiple regression was performed using the following as independent variables: fresh gas flow, duration of agent administration, the inverse of the square root of time ($1/\sqrt{t}$), age, mass, height, sex, ASA status, MF_A, body temperature change, F_A/F_D. A backward selection method was used with a threshold F-ratio of 4 for entry-to/removal-from the linear regression model.

Results

Patient details are shown in Table 2. In total, 302 patients participated in the study and their distributions among the 12 groups were similar. There were no differences in age, mass, height, body mass, body mass index, MF_A, temperature change, or duration of anaesthetic administration.

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*Supplementary material is available to subscribers with the on-line version of the journal at the journal website.

Table 4 Detailed results of measurements for the four volatile agents. Patients are grouped according to administered agent and fresh gas flows $\dot{V}_F$=fresh gas flow, MF_A=mean expired partial pressure obtained by averaging the end-tidal partial pressures of anaesthetic agent (kPa) recorded every 5 s. Ratios of volatile agent partial pressures F_A/F_I=end-tidal to inspired. F_I/F_D=inspired to fresh gas flow. F_A/F_D=end-tidal to fresh gas flow. Change in temperature=difference in body temperature between beginning and end of the procedure. *Significant differences between $\dot{V}_F$ of 0.5 and 1 litre min^{-1} $^{+}$Significant differences between $\dot{V}_F$ of 0.5 and 3 litre min^{-1} †Significant differences between $\dot{V}_F$ of 1 and 3 litre min^{-1} ‡Significant differences between 'wash-in' values and values achieved during maintenance of stable anaesthesia.

Agent	$\dot{V}_F$ (litre min^{-1})	MF_A (kPa)	Agent used (g)	Agent consumption rate (g min^{-1})	F_A/F_I		F_I/F_D		F_A/F_D		Change in temperature (°C)
					Wash-in	Steady state	Wash-in	Steady state	Wash-in	Steady state	
Desflurane	0.5, n=26	4.3 (0.9)	39.9^{+} (24.7)	0.39^{*+} (0.22)	0.91 (0.13)	0.94 (0.03)	0.80 (0.14)	0.76 (0.12)	0.74 (0.17)	0.72 (0.12)	0.3 (0.6)
	1, n=26	4.0 (0.8)	$51.8^{\dagger}$ (31.9)	$0.67^{*\dagger}$ (0.50)	0.92 (0.05)	0.95 (0.03)	0.80 (0.13)	0.82 (0.10)	0.74 (0.13)	0.77 (0.10)	0.3 (1.2)
	3, n=24	4.1 (0.7)	$85.5^{+\dagger}$ (47.6)	$1.05^{+\dagger}$ (0.21)	0.92 (0.08)	0.94 (0.04)	0.84 (0.10)	0.81 (0.05)	0.77 (0.13)	0.76 (0.05)	0.1 (0.6)
Enflurane	0.5, n=23	1.0 (0.2)	26.4^{+} (16.2)	0.37^{+} (0.21)	0.71 (0.07)	0.74^{*} (0.09)	0.78 (0.17)	0.48^{*+} (0.16)	0.55 (0.12)	0.35^{*+} (0.12)	0.2 (0.7)
	1, n=25	1.3 (0.3)	35.4 (25.5)	0.43 (0.25)	0.72 (0.09)	0.80^{*} (0.09)	0.81 (0.13)	$0.65^{*\dagger}$ (0.15)	$0.58^{\ddagger}$ (0.12)	$0.52^{*\dagger}$ (0.14)	0.1 (0.6)
	3, n=24	1.2 (0.3)	51.0^{+} (35.9)	0.51^{+} (0.28)	$0.68^{\ddagger}$ (0.06)	0.78 (0.06)	0.84 (0.10)	$0.84^{+\dagger}$ (0.09)	$0.57^{\ddagger}$ (0.9)	$0.66^{+\dagger}$ (0.09)	0.5 (0.7)
Halothane	0.5, n=25	0.8 (0.7)	27.3 (26.8)	0.36 (0.40)	$0.67^{\ddagger}$ (0.08)	0.74 (0.10)	$0.74^{\ddagger}$ (0.23)	0.38^{*+} (0.14)	$0.49^{\ddagger}$ (0.17)	0.28^{*+} (0.12)	0.2 (0.6)
	1, n=27	0.7 (0.1)	26.6 (19.4)	0.43 (0.47)	$0.68^{\ddagger}$ (0.13)	$0.78^{\dagger}$ (0.07)	$0.76^{\ddagger}$ (0.20)	$0.59^{*\dagger}$ (0.18)	$0.53^{\ddagger}$ (0.19)	$0.46^{*\dagger}$ (0.16)	0.2 (0.4)
	3, n=24	0.7 (0.2)	33.3 (19.3)	0.38 (0.21)	0.70 (0.12)	$0.72^{\dagger}$ (0.07)	0.76 (0.21)	$0.79^{+\dagger}$ (0.14)	$0.51^{\ddagger}$ (0.13)	$0.57^{+\dagger}$ (0.13)	0.1 (0.5)
Isoflurane	0.5, n=26	0.9 (0.2)	15.7^{+} (7.1)	0.26^{+} (0.15)	$0.75^{\ddagger}$ (0.07)	0.84 (0.07)	$0.74^{+\ddagger}$ (0.20)	0.55^{*+} (0.15)	$0.55^{\ddagger}$ (0.16)	0.47^{*+} (0.15)	0.2 (0.5)
	1, n=25	0.9 (0.2)	$20.8^{\dagger}$ (9.9)	0.36 (0.22)	$0.74^{\ddagger}$ (0.07)	0.80 (0.05)	$0.78^{\ddagger}$ (0.15)	$0.69^{*\dagger}$ (0.12)	0.57 (0.12)	$0.55^{*\dagger}$ (0.11)	0.2 (0.6)
	3, n=26	1.0 (0.2)	$36.7^{+\dagger}$ (23.0)	0.50^{+} (0.57)	$0.75^{\ddagger}$ (0.06)	0.81 (0.07)	0.85^{+} (0.08)	$0.85^{+\dagger}$ (0.10)	$0.63^{\ddagger}$ (0.06)	$0.69^{+\dagger}$ (0.10)	0.5 (0.8)

Distribution of ASA status was equal among the groups and the male:female ratios did not differ. There were equivalent numbers of patients at sea level and at altitude.

Table 3 summarizes the significant differences in rate of agent consumption, and the partial pressure ratios (F_A/F_D, F_I/F_D, and F_A/F_I) that were found between the three $\dot{V}_F$ groups. Table 4 presents the results in detail. At the flows studied, desflurane consumption rate depended on $\dot{V}_F$. In contrast, the halothane consumption rate was not influenced by $\dot{V}_F$. Isoflurane and enflurane showed differences in consumption rates when flows of 0.5 and 3 litre min^{-1} were compared. For these two agents there were no differences between flows of 0.5 *vs* 1 litre min^{-1}, and between 1 *vs* 3 litre min^{-1}. An incidental finding was that patients at altitude (>1300 m) required significantly greater end-expired partial pressures of volatile anaesthetic agent (MF_A) than those at sea level (Fig. 1).

On comparing the partial pressure ratios after the intitial, 10-min, high-$\dot{V}_F$ wash-in period with those during anaesthetic maintenance, the following were found (Tables 3 and 4). Desflurane: no significant differences in F_A/F_I, F_I/F_D, and F_A/F_D. This indicates that the wash-in period was sufficient to have achieved steady state, allowing reduction of $\dot{V}_F$ with little or no adjustment to vaporizer settings. For the other three agents, there were small, but statistically significant differences in F_A/F_I indicating that, the 10-min wash-in phase allowed reduction of $\dot{V}_F$, if vaporizer settings were increased (as revealed by increased F_I/F_D ratios). With regard to the F_I/F_D ratios, there were differences in the low and minimal flow groups. These differences confirmed that vaporizer settings had to be increased when reducing $\dot{V}_F$. F_A/F_D differences were broadly similar to F_I/F_D differences with the same interpretation.

Stepwise linear regression

Factors associated with agent consumption were sought by stepwise linear regression modelling. Results for volatile agent total consumption and consumption rate are presented in Tables 5 and 6. $\dot{V}_F$ and duration of administration were included in the regression models for total consumption for all four agents. In addition, enflurane total consumption was influenced by MF_A, F_A/F_D at steady state, patient height, and change in body temperature. Total halothane consumption was also affected by patient height, sex, age, and ASA status; isoflurane by altitude, temperature change, and body mass.

$\dot{V}_F$ affected the consumption rate of desflurane, enflurane, and isoflurane, but not halothane. MF_A influenced the consumption rates of desflurane and halothane. $1/\sqrt{t}$ affected the consumption rates of enflurane and isoflurane. The halothane consumption rate was also affected by duration of anaesthesia and isoflurane rate by patients' sex and altitude.

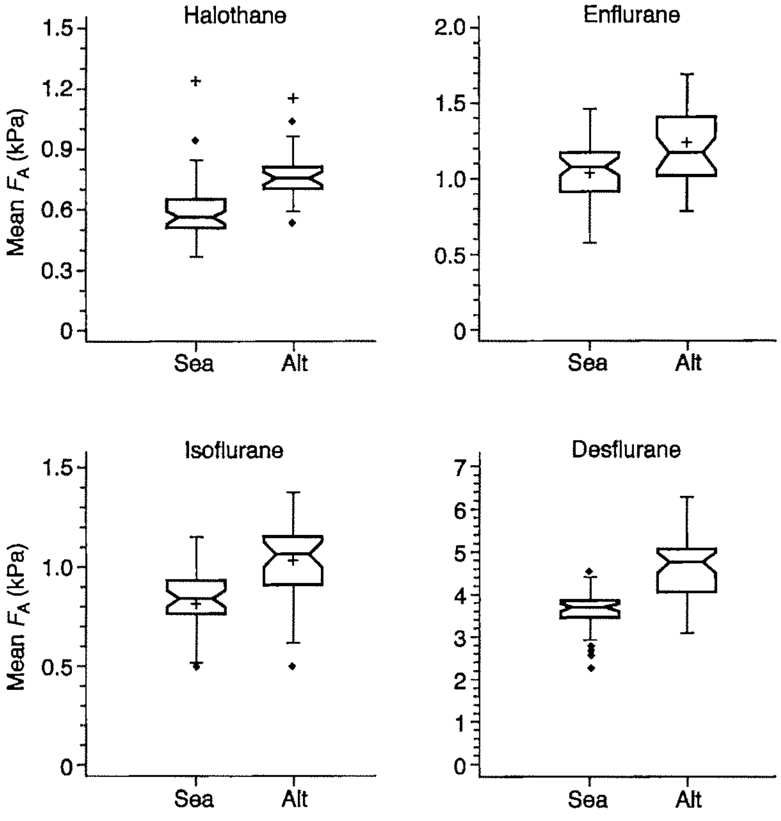

Fig 1 Box and whisker plots of mean expired partial pressures measured in patients at sea level and altitude. Mean F_A=mean expired partial pressure obtained by averaging the end-tidal partial pressures of anaesthetic agent (kPa) recorded every 5 s. Sea=sea level; Alt=altitude greater than 1300 m. Explanation of the plots: the ends of the 'box' illustrate the 25th and 75th percentiles and the horizontal line within the box depicts the median value. The 'notch' represents the 95% confidence interval of the median The 'whiskers' illustrate the range.

Table 5 Results of stepwise linear regression for consumption (g) of volatile anaesthetic $\dot{V}_F$=fresh gas flow (0 5, 1 0, and 3 0 litre min^{-1}). MF_A=mean expired partial pressure obtained by averaging the end-tidal partial pressures of anaesthetic agent (kPa) recorded every 5 s. Duration=duration of volatile anaesthetic agent administration (min). Altitude was coded as 0=sea level, 1=>1300 m Sex was coded as male=1, female=0 F_A/F_D=volatile agent ratio of end-tidal to fresh gas flow partial pressures at 'steady state' Height=patient height (cm) Temp change=change in body temperature (°C) between beginning and end of procedure. Weight=body mass (kg)

Agent	Independent variables	Coefficient	SEM	Significance level	R^2	Durbin–Watson statistic
Desflurane	V_F	20 10	2.27	<0 001	0.85	1.63
	Duration	0 310	0.03	<0 001		
Enflurane	V_F	13.7	2 20	<0 001	0.94	1.73
	MF_A	39 30	9 7	<0 001		
	Duration	0.20	0 03	<0.001		
	F_A/F_D	–48.7	15 3	<0.01		
	Height	0–0.16	0.06	<0.01		
	Temp change	12 4	2.70	<0.001		
Halothane	V_F	4.9	1.70	<0.01	0.82	2.01
	Duration	0 11	0.04	<0.01		
	Height	0 10	0 04	0.021		
	Sex	–14.8	4 0	<0 001		
	Age	0 69	0.18	<0 001		
	ASA status	–8 1	3 3	0 018		
Isoflurane	V_F	5 3	1 20	<0 001	0.89	2.41
	Duration	0.11	0 02	<0 001		
	Altitude	4 5	2.5	0 073		
	Weight	0.06	0.04	0 19		
	Temp change	5 8	2.0	<0.01		

Table 6 Results of stepwise linear regression for consumption rate (g min^{-1}) of volatile anaesthetic agents: V_F=fresh gas flow (0.5, 1.0, and 3 0 litre min^{-1}) MF_A=mean expired partial pressure obtained by averaging the end-tidal partial pressures of anaesthetic agent (kPa) recorded every 5 s Duration=duration of volatile anaesthetic agent administration (min) $1/\sqrt{t}$=inverse of the square root of time (min^{-1}) Altitude was coded as 0=sea level, 1=>1300 m. Sex was coded as male=1, female=0 FGF, fresh gas flow

Agent	Independent variables	Coefficient	SEM	Significance level	R^2	Durbin–Watson statistic
Desflurane	MF_A	0.07	0.01	<0.001	0.94	1 85
	V_F	0.26	0.02	<0 001		
Enflurane	$1/\sqrt{t}$	2.57	0 24	<0 001	0.91	1.32
	FGF	0.09	0.02	<0 001		
Halothane	MF_A	0.65	0.11	<0 001	0.57	1.97
	Duration	−0.001	0.00	0.137		
Isoflurane	$1/\sqrt{t}$	0.06	0.021	0.005	0 81	2.46
	FGF	3.17	0.5	<0.001		
	Sex	−0.10	0 04	0.018		
	Altitude	0.08	0 05	0 118		

Discussion

The finding that $\dot{V}_F$ did not influence halothane consumption is unexpected. Furthermore desflurane was the only agent where usage was affected by $\dot{V}_F$ settings. Consumption of moderately soluble drugs (enflurane and isoflurane) was less influenced by $\dot{V}_F$ than in the case of desflurane. There was no clear distinction in the consumption rates of enflurane and isoflurane between $\dot{V}_F$ of 0.5 and 1.0 litre min^{-1} and between 1 and 3 litre min^{-1}. In this study, all the anaesthetic machines were identical (Dräger, model 'Julian') so that equipment of features (e.g. breathing circuit time-constants, inflow and outflow placements, mode of excess gas venting) could not affect agent consumption and partial pressure dynamics.[12 13]

Recognizing that all three V_F allowed significant recycling of exhaled gases, these apparent disparities can be explained as follows. To maintain a desired end-tidal (alveolar) partial pressure it is necessary to compensate for tissue uptake. For halothane this is considerable[14] because its high tissue solubility increases uptake into peripheral organs (e.g. muscle) and furthermore a considerable proportion of halothane undergoes hepatic metabolism.[14 15] It is therefore necessary to deliver a minimum amount of drug per unit time to compensate for uptake into the blood. This can be effected by either supplying the inhaled drug using a greater $\dot{V}_F$ containing a partial pressure that is equal to (or close to) the desired inhaled value, or by using a greater partial pressure at low $\dot{V}_F$. Either way, a certain rate of delivery of agent to the breathing system is needed to maintain inhaled partial pressures.

This phenomenon may be explained using Mapleson's hydraulic, pharmacokinetic model for volatile agent uptake.[16] In Figure 2, uptake and distribution of volatile anaesthetic vapour is shown by a series of interconnected cylinders where the fluid heights represent vapour partial pressures. Volumes of distribution are depicted by the base areas, amounts of drug by fluid volumes, and drug clearances by the diameters of the various PIPES. Fresh gas partial pressure is shown by the height of the cylinder at the extreme left (F_D), which is full at all times and $\dot{V}_F$ is represented by the diameter of its outlet. Inspired partial pressure is portrayed by the height of fluid in cylinder F_I from which excess vapour may spill over during high $\dot{V}_F$ (analagous to the spill-valve of a ventilator). This spill-over is considerable during high $\dot{V}_F$, minimal during low $\dot{V}_F$ and absent during closed-circuit anaesthesia. Two large peripheral compartments (muscle, fat) drain agents away from the lungs (F_A), and viscera (including the brain). To maintain a constant level in the brain, it is necessary to supply drug to F_A from F_I to prevent the level in F_A from falling. Removal of drug from F_I can in turn be replaced by supplying drug from F_D using a high $\dot{V}_F$ containing a low partial pressure and this is represented in the upper illustration of Figure 2 by a short cylinder, F_D delivering fluid to F_I via a wide diameter pipe of high conductance. On changing to low flow (thin outlet pipe from F_D), the same amount of drug per unit time must be delivered to the breathing system and lungs by an increased pressure in F_D. This is shown in the lower illustration in Figure 2 by the tall cylinder, F_D delivering fluid to F_I via a small diameter pipe of low conductance. In this manner the fluid level in F_I and, therefore, in F_A and the viscera is maintained. The dotted lines in the lower illustration in Figure 2 show how the partial pressures in F_I and F_A decrease if the partial pressure in F_D is not increased.

In the case of the lower illustration in Figure 2 where the spill-over is minimal, changes to the properties of the peripheral cylinders and the PIPES connecting them to F_A will have a large influence on 'drug' disposition. For example, an increase in uptake by the peripheral cylinders will decrease the level in F_A and, therefore, in the viscera (brain). This can be compensated for by increasing flow to F_A by increasing the height of the level in F_I. This in turn can be brought about by increasing the height of fluid in cylinder F_D to increase delivery of drug to F_I, with no extra spill-over occurring at F_I. It is under such circumstances that 'patient factors' become major determinants of drug consumption during low-flow anaesthesia.

We suggest that with regard to halothane in this study, continuing uptake of drug was so rapid that at the three $\dot{V}_F$

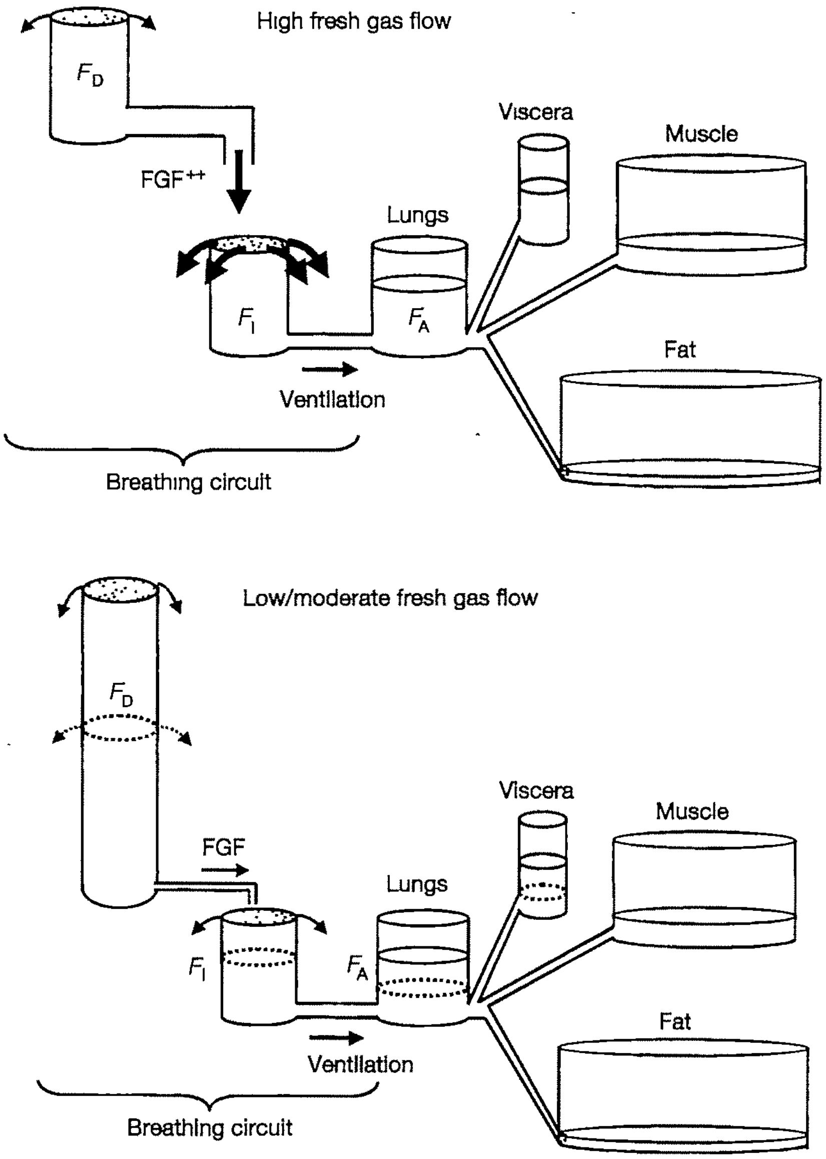

Fig 2 Hydraulic analogue model of uptake and distribution of volatile anaesthetic agent from a circle breathing system (modified from Mapleson[16]). Agent partial pressures are represented by the heights of fluid in the cylinders. The anaesthetic breathing circuit is the two cylinders on the left (F_D and F_I) that deliver drug to the central cylinder, the alveoli (F_A), from which drug is distributed to peripheral compartments Vapour is introduced into the system from the cylinder on the far left (F_D), which is kept full at all times. The partial pressure of the delivered vapour is represented by the height of cylinder F_D and that of the inhaled vapour by the height of fluid in cylinder F_I. Excess vapour vented from the breathing system is depicted by spill-over from cylinder F_I. Fresh gas flow rate and excess vapour spill-over are represented by the associated arrows. F_D=delivered (fresh gas) partial pressure; F_I=inspired partial pressure, F_A=alveolar partial pressure, FGF=fresh gas flow. The upper illustration depicts vapour delivered at a low partial pressure (short cylinder F_D) by a high fresh gas flow rate (thick outlet pipe from F_D) with large amounts of excess agent drug spilling out of the breathing system at F_I. The lower illustration depicts vapour delivered at a high partial pressure (tall cylinder F_D) at a low fresh gas flow rate (narrow outlet pipe from F_D) with little excess agent being vented Inhaled and alveolar partial pressures are thereby maintained at the same levels as in the upper illustration The dotted lines in the lower illustrate that if the partial pressure of F_D is reduced while maintaining a low fresh gas flow, the inspired (and therefore alveolar) partial pressures decrease to below targeted values.

studied, there was little venting (spill-over) of vapour via expired gas to the atmosphere, and patient factors became important determinants of drug consumption. This conclusion is strengthened by the following considerations.

- F_A/F_I was 0.75 at all $\dot{V}_F$, indicating that during anaesthetic maintenance, transfer from alveoli to blood was a continuing process The re-circulation of alveolar gas containing reduced amounts of halothane vapour to the breathing system resulted in decreased F_I/F_D and F_A/F_D ratios, and these varied with $\dot{V}_F$ (Tables 3 and 4).
- At low and minimal flows, halothane F_A/F_I and F_A/F_D ratios were small (Table 4) so that the vented gas contained reduced amounts of vapour. (At reduced $\dot{V}_F$,

Table 7 Sites of the academic hospitals where the study was conducted, heights above sea level and atmospheric pressures. Atmospheric pressures are the mean of the monthly averages during 1998 (by courtesy of the South African Weather Bureau)

City	Altitude (m)	Ambient pressure (kPa)	SD	Academic hospitals
Bloemfontein	1351	86.98	0.23	University of the Orange Free State
Cape Town	44	101.25	0.28	University of Cape Town, University of Stellenbosch
Durban	8	101.49	0.28	University of Natal
Johannesburg	1694	83.35	0.17	University of the Witwatersrand
Pretoria	1330	87.38	0.22	Medical University of South Africa, University of Pretoria

gas vented from a circle-system is composed mainly of expired gas).

- No differences in halothane consumption rate were found at the three $\dot{V}_F$.
- Stepwise linear regression indicated that although $\dot{V}_F$ did indeed influence halothane usage, patient descriptors were also strongly associated.

At the other extreme, continuing uptake of desflurane, a much less soluble drug is markedly decreased during anaesthetic maintenance. Therefore, $\dot{V}_F$ strongly influences desflurane consumption at all flow rates because surplus is lost to the atmosphere. This conclusion is strengthened by the following considerations.

- F_A/F_I was 0.94 at all $\dot{V}_F$, indicating that at 'steady state', transfer of desflurane from alveoli to blood was small.
- F_I/F_D and F_A/F_D ratios were high (0.8 and 0.75, respectively), indicating that re-circulated exhaled gas contained concentrations of desflurane vapour that were close to the inspired values. Furthermore, these ratios were uninfluenced by $\dot{V}_F$ (Tables 3 and 4). These high F_A/F_I and F_A/F_D ratios, resulted in vented gas containing significant amounts of vapour even at low and minimal flows.
- Significant differences in desflurane consumption rate were measured at the three $\dot{V}_F$.
- Stepwise linear regression revealed that $\dot{V}_F$ was a major determinant of desflurane consumption but patient descriptors were not associated with drug usage.

The drugs of intermediate solubility, isoflurane and enflurane, lie between the two extremes. Agent consumption was significantly less when comparing V_F of 0.5 and 3.0 litre min^{-1}, but there were no differences in consumption between $\dot{V}_F$ of 0.5 and 1.0 litre min^{-1} and between 1.0 and 3.0 litre min^{-1}. Consumption of these two drugs was also, like halothane, associated with certain patient descriptors (Tables 5 and 6). Lowe[17] has shown that during totally closed-circuit anaesthesia, volatile agent consumption rate is directly related to the square root of time in accordance with the exponentially decreasing uptake of agent over time. This variable played a role in the regression models for enflurane and isoflurane under conditions of partial rebreathing, which suggests that at these low flows, venting of expired vapour from the circle-system was minimal.

Mathematical models have been useful in predicting theoretical uptake and consumption of various agents for comparative purposes,[1–3] but they assume a constant alveolar partial pressure requirement and fixed patient variables that influence agent uptake (e.g. cardiac output, ventilation). In reality, these factors vary during clinical anaesthesia. For example, alveolar partial pressure requirements may increase during surgical stimulations or decreased by supplementary drugs such as nitrous oxide, opioids, and alpha-receptor agonists. Stepwise linear regression revealed statistically significant associations between volatile agent consumption and various patient descriptors. However, it cannot be construed from our data that these are causative. Our results merely indicate that other variables besides $\dot{V}_F$ influence agent consumption and prospective studies will be necessary to identify the patient characteristics and surgical conditions that determine drug uptake.

Circle-systems are often used at inappropriately high $\dot{V}_F$ and repeated recommendations have been made for the reduction of $\dot{V}_F$ in order to reduce costs.[2 4–7 18–21] This study confirms the well known phenomenon that during low $\dot{V}_F$ there are discrepancies between vaporizer settings and inspired (or end-tidal) vapour partial pressures[22 23] which is more marked with soluble agents and at low flows. Low flow anaesthesia should, therefore, be practised using agent monitors. In developing countries, halothane is the mainstay of anaesthesia and agent monitors are seldom available. This study, suggests that a $\dot{V}_F$ of less than 3 litre min^{-1} should not be used without agent monitors. Furthermore, a potential danger of halothane overdose is present when using low $\dot{V}_F$ without an agent monitor, if the anaesthetist increases $\dot{V}_F$ and forgets to reduce the vaporizer setting.

In contrast to the more soluble drugs, F_A/F_D and F_I/F_D for desflurane were similar, predictable, and independent of $\dot{V}_F$ (0.7–0.8). Furthermore this study supports previous work that desflurane usage can be reduced when given using minimal $\dot{V}_F$.[1 6 23 24] Considering the predictablity of desflurane partial pressures, perhaps agent monitoring is not mandatory because the setting of the precision vaporizer can be used to indicate the alveolar partial pressure.[1] This is not recommended because under- or overdosage could result if the vaporizer was faulty.

A wash-in period of 10 min at high $\dot{V}_{\mathrm{F}}$ (4.5 litre min^{-1}) was used. This is less than the usually recommended 15–20 min for minimal flow.[25] If this were inadequate, a marked difference between $F_{\mathrm{A}}/F_{\mathrm{I}}$ at the end of the wash-in period and during anaesthetic maintenance at low $\dot{V}_{\mathrm{F}}$ would have occurred. No difference was found with desflurane. Differences were found with the other three drugs (Table 4) but these differences were small and were easily compensated for by adjustments to the vaporizers. We conclude that even for the most soluble drug, halothane, a 10-min wash-in period was sufficient. For desflurane, an even shorter wash-in period will suffice [3 14 23 24 26] with even greater cost savings.

Three of the participating hospitals were in coastal cities whereas the remainder were situated inland, more than 1300 m above sea level at reduced atmospheric pressures (Table 7). It was therefore possible to study the influence of altitude on MF_{A} and on agent consumption. On pooling and comparing the patients' mean end-tidal partial pressures of volatile agents according to whether they were anaesthetized at sea level or altitude, it was found that those who had undergone surgery at altitude required greater end-tidal partial pressures of all four volatile agents. In the present study, anaesthesia was with a combination of approximately 66% nitrous oxide and a volatile agent. Furthermore, anaesthesiologists in the seven different institutions were requested to administer anaesthesia as they normally would in their everyday practices, titrating volatile agent partial pressures according to patient requirements. Our findings therefore possibly reflect the reduced effectiveness of nitrous oxide at altitude. It has been demonstrated that at decreased ambient pressures, nitrous oxide causes less analgesia[27] and is a less efficient anaesthetic,[28] and nitrous oxide is also probably less effective as an adjuvant. As far as we are aware, this may be the first documented evidence for this hypothesis, considering that the only other anaesthetic adjuvant administered was a small dose of fentanyl.

We conclude that under clinical circumstances, using moderate and low $\dot{V}_{\mathrm{F}}$, consumption of relatively soluble volatile anaesthetic agents depends only partially on $\dot{V}_{\mathrm{F}}$ and that monitoring agent partial pressures within the breathing system is highly desirable. On the other hand, the $F_{\mathrm{A}}/F_{\mathrm{D}}$ of desflurane is predictable and independent of $\dot{V}_{\mathrm{F}}$. The contribution of nitrous oxide to anaesthesia is weakened at altitude.

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Intrinsic positive end-expiratory pressure during one-lung ventilation of patients with pulmonary hyperinflation. Influence of low respiratory rate with unchanged minute volume[†]

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Background. We measured lung mechanics and gas exchange during one-lung ventilation (OLV) of patients with chronic obstructive pulmonary disease, using three respiratory rates (RR) and unchanged minute volume.

Methods. We studied 15 patients about to undergo lung surgery, during anaesthesia, and placed in the lateral position. Ventilation was with constant minute volume, inspiratory flow and $F_{I_{O_2}}$. For periods of 15 min, RR of 5, 10, and 15 bpm were applied in a random sequence and recordings were made of lung mechanics and an arterial blood gas sample was taken. Data were analysed with the repeated measures ANOVA and paired *t*-test with Bonferroni correction.

Results. Pa_{O_2} changes were not significant. At the lowest RR, Pa_{CO_2} decreased (from 42 (SD 4) mm Hg at RR 15–41 (4) mm Hg at RR 10 and 39 (4) mm Hg at RR 5, $P<0.01$), and end-tidal carbon dioxide increased (from 33 (5) mm Hg at RR 15 to 35 (5) mm Hg at RR 10 and 36 (6) mm Hg at RR 5, $P<0.01$). Intrinsic positive end-expiratory pressure (PEEPi) was reduced even with larger tidal volumes (from 6 (4) cm H_2O at RR 15–5 (4) cm H_2O at RR 10, and 3 (3) cm H_2O at RR 5, $P<0.01$), most probably caused by increased expiratory time at the lowest RR.

Conclusion. A reduction in RR reduces PEEPi and hypercapnia during OLV in anaesthetized patients with chronic obstructive lung disease.

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To facilitate thoracic surgery, one-lung ventilation (OLV) is a valuable technique. One lung is mechanically ventilated while the other is either occluded, or left open to the atmosphere. Generally a dependent lung tidal volume (V_t) similar to that used in two-lung ventilation is recommended.[1] Respiratory frequencies around 15 bpm are commonly used during OLV.[1] Other authors recommend that the dependent lung should be ventilated with a tidal volume of 10–12 ml kg^{-1} and the respiratory rates (RR) to maintain the arterial partial pressure of carbon dioxide (Pa_{CO_2}) at normal values.[2] These suggestions do not consider that many patients having lung surgery have chronic obstructive pulmonary disease (COPD) with airflow limitation and pulmonary hyperinflation. During the OLV of these patients, intrinsic positive end-expiratory pressure (PEEPi) is often present, and can be increased by an unfavourable ventilatory pattern.[3] Moreover, COPD patients have increased physiological dead space and can develop hypercapnia.

During the mechanical ventilation of these patients' lungs, conditions that impede expiratory flow (increased airway resistance, and the resistance of the double-lumen

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tube (DLT))[4 5] or poor settings of the ventilator[6] may cause dynamic pulmonary hyperinflation (DPH) and PEEPi. In addition, alveolar overdistension by severe DPH in the ventilated lung may divert pulmonary blood flow to the non-ventilated lung, and impair arterial oxygenation.

Increases in RR, V_t, or a reduction of expiratory time (T_e) would encourage the development of PEEPi and DPH.[7] Severe DPH causes circulatory depression and pulmonary barotrauma.[4 7 8]

The settings for mechanical ventilation in patients with COPD during OLV to avoid excessive DPH and hypercapnia have not been clearly identified. Studies performed during OLV have mainly assessed the effect of V_t changes[9 10] or the isolated effect of altered RR with unchanged V_t.[11] However, with constant RR, a greater V_t would promote PEEPi,[6] while a smaller V_t would not be adequate because of dependent lung atelectasis and hypercapnia. If a constant V_t is chosen, with changes in RR, then an increase of RR would cause PEEPi and a decrease of RR would increase hypercapnia because of reduced minute ventilation. We tested if a ventilatory pattern, which combined a reduction in RR with a constant minute volume (with a proportional V_t increase), could control both hypercapnia and PEEPi during OLV of patients with chronic obstructive pulmonary disease.

Materials and methods

The Institutional Review Board approved the investigation and informed consent was obtained from 15 patients undergoing elective thoracotomy for tumour resection and requiring OLV. Before surgery, pulmonary function was tested in the sitting position, including spirometry and static lung volumes determined by plethysmography (MasterScreen Body™, Jaeger and Toennies™, Erich Jaeger GmbH, Hoechberg, Germany). Only patients whose preoperative functional residual capacity (FRC) exceeded 120% of the predicted value were included in the study. Patient details and pulmonary function values are shown in Table 1.

Table 1 Patient details and preoperative pulmonary function tests. FEV1, forced expiratory volume in 1 s

	Mean **(n=15)**	SD
Age (yr)	63 (54-72)	9
Height (cm)	173	8
Weight (kg)	78	16
FEV1 (% predicted)	68	12
FRC (% predicted)	162	42
RV (% predicted)	183	62
Pa_{CO_2} (mm Hg) room air, supine	38	4
Pa_{O_2} (mm Hg) room air, supine	77	10

In all patients, anaesthesia was induced and maintained with a variable rate continuous infusion of propofol (loading dose 2 mg kg^{-1}) followed by continuous infusion of 3–5 mg kg^{-1} h^{-1}) and inhalation of isoflurane (<0.5 MAC). Epidural analgesia at the mid-thoracic level (Th5–Th8) (test dose of 3 ml 2% lidocaine with epinephrine 1/200 000 followed by a continuous infusion of bupivacaine 0.5% 2–5 ml h^{-1}) was started before induction of general anaesthesia and maintained continuously during surgery. Pancuronium (loading dose of 80 µg kg^{-1} and top up doses of 20 µg kg^{-1}) was used to allow tracheal intubation and to maintain neuromuscular block throughout surgery. The neuromuscular block was assessed by regular measurements of post-tetanic count during the procedure. A three-lead electrocardiogram, invasive radial arterial pressure and arterial oxygen saturation were monitored continuously. The Datex® Ultima™ SV capnometer (Datex Instrumentarium, Helsinki, Finland) was used to measure expired end-tidal carbon dioxide tension (E'_{CO_2}), flow-volume and pressure–volume loops. In all patients, the bronchus of the dependent lung was intubated with an appropriate size (based on sex and height of the patients)[12] DLT (Broncho-cath™, Mallinckrodt Laboratories, Athlone, Ireland). This was correctly positioned using fiberoptic bronchoscopy, first in the supine position and then in the lateral position. The patients' lungs were ventilated with 50% oxygen in air, with a constant inspiratory flow ventilator (Siemens Servo 900 C; Siemens Elema; Solna, Sweden). Initial settings were V_t 10 ml kg^{-1} and a rate of 10 bpm. External positive end-expiratory pressure (PEEP) was set to zero. Inspiratory time (T_i) was 33% of total cycle time (T_{tot}) and end-expiratory pause was 10% (of T_{tot}). The ventilator and the breathing system were inspected carefully and checked for potential leaks. After turning the patient in the lateral position and checking of the correct position of the DLT by bronchoscopy, the tracheal limb of the DLT was clamped and opened to the atmosphere to allow lung collapse. Three ventilatory rates of 5, 10 and 15 bpm (RR 5, RR 10, RR 15) were applied in a random sequence and maintained for 15 min. After each 15-min period, end-inspiratory and end-expiratory occlusions were performed to measure elastance and intrinsic positive pressure, and arterial blood gas samples were drawn. The occlusions were maintained until the airway pressure was stable.[6] The airway pressure was recorded with an ink recorder (Gould Brush 2600, Gould Inc., Instrument Systems Division, Cleveland, OH, USA) with a paper speed of 25 mm s^{-1}. Blood gas samples were analysed immediately after they were drawn, then corrected according to the patient's temperature, with the Synthesis® 350 (Instrumentation Laboratory, Milan, Italy) blood gas analyser.

From the recorded data, the elastic recoil pressure (Pel,rs) of the dependent lung-thorax was determined by subtracting the recorded PEEPi from the static end-inspiratory pressure. Static compliance of the respiratory system (Cst,rs) was obtained by dividing the expiratory tidal volume by Pel,rs. The exhaled volume was corrected for the compliance of the respiratory circuit (7 ml cm H_2O^{-1}) to eliminate errors from the volume compressed in the tubing.[13]

Table 2 Respiratory mechanics and blood gas values during the three RRs. Values are mean (SD). Student's *t*-test with Bonferroni adjustment for multiple comparisons. *$P<0.01$ comparing RR 10 with RR 15. †$P<0.01$ comparing RR 5 with RR 10. +$P<0.01$ comparing RR 5 with RR 15. Pel, elastic recoil pressure

	RR 5	**RR 10**	**RR 15**	***P*-values repeated measures ANOVA**
V_t (ml)	1234 (197)$^+$	623 (97)†	433 (81)*	
P_{peak} (cm H_2O)	33 (5)$^+$	26 (6)†	24 (5)*	<0.01
$P_{plateau}$ (cm H_2O)	21 (5)$^+$	17 (6)†	14 (5)*	<0.01
PEEPi (cm H_2O)	3 (3)$^+$	5 (4)†	6 (4)	<0.01
Pel (cm H_2O)	18 (6)$^+$	11 (6)†	7 (5)*	<0.01
Crs,st (ml cm H_2O^{-1})	82 (41)	75 (38)	97 (83)	NS
E'_{CO_2} (cm H_2O)	36 (6)$^+$	35 (5)†	33 (5)*	<0.01
Pa_{CO_2} (mm Hg)	39 (4)$^+$	41 (4)†	42 (4)	<0.01
Pa_{O_2} (mm Hg)	200 (58)	193 (65)	191 (69)	NS
Pa_{CO_2}–PE'_{CO_2}	2 (3)$^+$	7 (5)†	8 (5)*	<0.01

The study was performed in the lateral position, before the surgical procedure started.

Statistical analysis

We used the Kolmogorov–Smirnov one-sample test to check that the samples were normally distributed. Repeated measures ANOVA was used to test for differences between RRs. Pairwise comparisons between groups were made, using Student's paired *t*-test with the Bonferroni adjustment for multiple comparisons, using the GB-Stat 6.0 for IBM and compatibles (Dynamic Microsystems, Inc., 1996). *P*-values <0.05 were considered significant. Data are presented as mean (SD).

Results

All the patients had mild pulmonary hyperinflation. The pulmonary function tests and blood gas values are shown in Table 1. The perioperative measured and calculated variables at the different RRs are shown in Table 2.

With a reduced RR and unchanged minute volume, V_t (and T_{tot} and expiratory time (T_e)) increased. These changes were proportional to the changes in the RR (i.e. ×2 or ×1.5). Peak inspiratory airway pressure (P_{peak}) and $P_{plateau}$ were significantly greater when the RR was decreased ($P<0.01$, repeated measures ANOVA).

Pel,rs increased at lower RR ($P<0.01$, repeated measures ANOVA), but Cst,rs did not change significantly (Table 2). During dependent-lung ventilation, PEEPi values greater than 10 cm H_2O were found in only two patients (at RR 10 and RR 15). Zero PEEPi values were recorded in four patients at RR 5 and another one at RR 10. Despite the larger V_t at lower RR, PEEPi was less ($P<0.01$, repeated measures ANOVA). This value was significantly less at RR 5 compared with RR 10 and RR 15 ($P<0.01$, Bonferroni *t*-test), but without statistical significance when comparing RR 15 and RR 10 (Table 2 and Fig. 1).

Arterial partial pressure of oxygen was not affected (Table 2). Pa_{CO_2} was less ($P<0.01$, Bonferroni *t*-test) at RR 5 in comparison with RR 15 or RR 10. FE'_{CO_2} increased ($P<0.01$, repeated measures ANOVA) when the RR was reduced (Table 2). Consequently, the arterial to end-tidal carbon dioxide partial pressure difference (Pa_{CO_2}–PE'_{CO_2}) was significantly less when the RR was small (Table 2).

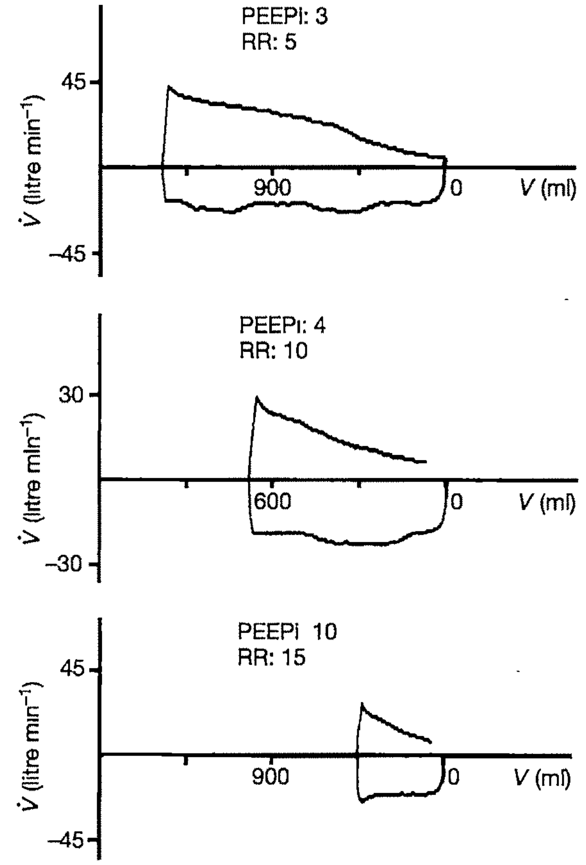

Fig 1 Flow-volume loop measured with the Datex Ultima SV Capnometer (Datex Instrumentarium, Helsinki, Finland) of one patient when changing the respiratory rate.

Discussion

Our main findings were a decrease of PEEPi when RR was reduced, along with a decrease in Pa_{CO_2} and Pa_{CO_2}–PE'_{CO_2}, and with an increased P_{peak}, $P_{plateau}$, and Pel,rs ($P<0.01$, repeated measures ANOVA) (Table 2 and Fig. 1).

Co-existing lung disease is the rule rather than exception in patients undergoing lung surgery. The volume, frequency and timing of gas delivered to the dependent lung can have important, disease-specific effects on the cardiovascular and respiratory systems.[14]

Until now, a low RR has not been studied during OLV in patients with pulmonary hyperinflation in a randomized fashion. Robinson and co-workers[15] describe two ventilator-dependent patients with cystic fibrosis who could not be managed with conventional ventilation during sequential double-lung transplantation. Lung implantation was facilitated by OLV at a slow rate (6 bpm) with a long T_i (5 s) and a long T_e (5 s), implantation of donor lung, by decreasing hypercapnia and reducing pulmonary arterial pressure.

Lowering the RR, with unchanged minute volume implies an increase in V_t. In patients without significant pulmonary disease, OLV during general anaesthesia decreases arterial oxygenation because of atelectasis in the dependent lung.[9] However, patients with COPD do not develop atelectasis and decrease in FRC during anaesthesia,[16] presumably because of long standing hyperinflation.

In obstructive airway disease, lung injury with alveolar leaks may be caused by dynamic hyperinflation during mechanical ventilation. Some authors believe that increased inspiratory airway pressures are necessary to overcome airway resistance when high inspiratory flow rates are used, as a large part of the inspiratory pressure is not transmitted to the alveoli.[17 18] Because alveolar distending volume is not readily measured clinically, $P_{plateau}$ measured during an inspiratory pause is generally accepted as a reasonable estimate of peak alveolar pressure.[19 20] During positive pressure ventilation, the $P_{plateau}$ below which lung injury is unlikely is approximately 35 cm H_2O, commonly believed to correspond to an alveolar pressure of approximately 30 cm H_2O. For safer OLV conditions, Slinger[21] suggested limiting $P_{plateau}$ to 25 cm H_2O. Given this range of opinion, careful monitoring of patients managed with this approach is mandatory. In the present study, the $P_{plateau}$ was generally less than this value (except a single value of 26 cm H_2O at RR 5) despite the V_t increases from 433 (81) ml at RR 15 to 623 (97) ml at RR 10 and 1234 (197) ml at RR 5. The duration of OLV periods in this study was short and the patients were anaesthetized and paralysed, but concern could arise from long-term use of low-rate ventilation.

At large values of V_t, an increased PEEPi might be expected, because in addition to the degree of airflow obstruction, one of the major determinants in the development of PEEPi is the V_t to be exhaled in a fixed fraction of time.[22] Nevertheless, besides V_t, the main determinant of dynamic hyperinflation and PEEPi in COPD patients is the absolute value of T_e and not the $T_i{:}T_{tot}$ ratio *per se.*[4] Therefore, considering a given respiratory system with its specific compliance and its expiratory and inspiratory resistances, for a fixed T_i fraction, PEEPi will increase when RR is raised (reduction of T_e) and decrease when the RR is reduced (increase of T_e). Small changes in T_e did not affect PEEPi because the volume expelled per unit time near the end of exhalation is very small.[23] In patients with COPD and acute respiratory failure, while PEEPi was increased by T_e shorter than 3 s, prolonging T_e more than 3 s had little effect on PEEPi.[6] Both studies were of mechanically ventilated patients with an acute exacerbation of COPD, and the effect of prolonging T_e on gas exchange were not assessed. In the present study of stable COPD patients during OLV in the lateral position, with constant inspiratory time fraction (T_i=33% of T_{tot}), a reduced RR and increased V_t, increased the T_e from 2.6 s at RR 15 to 4 s at RR 10 and 8 s at RR 5 bpm, respectively. In contrast to the findings of Rossi, because of the parallel increase of V_t in our study, a decrease of PEEPi was observed only at the very long T_e associated with the RR 5 bpm (Table 2 and Fig. 1).

An insignificant increase of Pa_{O_2} when RR was decreased (and V_t increased) supports the results of previous studies.[9–11] Increased inspiratory airway pressures causing increased vascular resistance in the dependent lung of some patients could explain the lack of consistently improved oxygenation during high V_t ventilation.[9 24]

In this study, the high RR (15 bpm) and small V_t ventilation caused hypercapnia with a mean Pa_{CO_2} of 43 mm Hg. When ventilation was performed at low RR (5 bpm) and high V_t, mean Pa_{CO_2} decreased significantly to 39 mm Hg. This value approached the preoperative values (38 (4) mm Hg). The reduced Pa_{CO_2}–PE'_{CO_2} suggests altered intrapulmonary gas distribution at low RR, but differences in E'_{CO_2} may also simply reflect the fact that, with a significant positive slope of the capnogram, prolonging expiration itself will increase E'_{CO_2} without necessarily reflecting any change in gas exchange.

This ventilatory pattern—lowered RR (and increased V_t) with constant minute volume—may represent a simple way to reduce PEEPi and hypercapnia during OLV in patients with pulmonary hyperinflation, as changing RR or V_t alone increases either the PEEPi, or the Pa_{CO_2}. Careful monitoring of these patients for the risk of barotrauma is mandatory. However, given the lack of significant effect on oxygenation (the hallmark of OLV), it is difficult to recommend the technique of high V_t, low RR OLV for routine practice. This ventilatory management should be reserved for patients with severe COPD in whom PEEPi and hypercapnia would possibly complicate OLV.

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Extreme value theory applied to postoperative breathing patterns

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Background. There has been little published work on the statistical features of breath times in postoperative patients. We applied extreme value theory (a statistical method) to the variation in the timing of postoperative breathing.

Methods. We observed 49 patients 3–6 h after a variety of surgical procedures, once they had achieved a stable breathing pattern. The breathing patterns could be one of the three types predicted by the extreme value model. 'Finite' breathing patterns (n=30) have a finite upper limit of duration for any apnoea. Patients that displayed one of the other two patterns ('standard' and 'extended') have, potentially, no limit in duration of apnoea.

Results. The type of breathing pattern observed in each patient was not reliably identified by most of the commonly used risk factors (age, type of surgery, opioid type, dose, and route of administration). A finite pattern was observed in 13 of 26 patients receiving epidural (*vs* 17 of 23 parenteral analgesia: P=0.15), and 15 of 19 receiving morphine (*vs* 15 of 30 other opioids: P=0.05). The patients with 'finite' patterns were also significantly less drowsy (score 1.04 (0.92) *vs* 1.62 (0.62), P<0.05).

Conclusions. The breathing pattern was not related to mean breath times, suggesting that the prevalence of apnoeas cannot be reliably predicted by measurement of the respiratory rate alone.

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Keywords: statistics, data analysis; lung, respiration; analgesics, opioid; statistics, extreme value theory

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It is well known that the duration of the breaths in postoperative patients may vary. Irregular unpredictable processes such as these are usually described statistically by using the probability distribution of a random variable. Surprisingly, there have been relatively few published reports describing the statistical modelling of these variations in postoperative breathing patterns.[1 2] A number of factors contribute to postoperative respiratory irregularities including the use of opioids for analgesia.[3]

Apnoeas can be described as breaths that have a very prolonged breath time (T_{TOT}) and can, therefore, be identified as points that lie in the right-sided 'tail' of the T_{TOT} frequency-distribution curve. There is a statistical method called extreme value theory, which describes the different possible 'tails' of frequency distributions.[4] The extreme value theory is concerned with probability calculations and the statistical inference associated with the extreme values of random processes It is widely used in the prediction of climatic processes (floods), financial events (insurance claims), and athletic records.[5] Tipett laid the theoretical foundations in 1928 when he showed that there could be only three possible types of extreme value limit distributions. The type I, or Gumbel distribution (which we will call the 'standard' distribution) has a tail that decays exponentially. It is found in data that follow normal and log normal distributions. In the type II, or Frechet (we term 'extended') distribution the tail decays more slowly than the exponential. The type III, or Weibull (we term 'finite'), distribution has a tail that decays more quickly approaching a finite upper limit. Gumbel wrote a seminal book in 1958 that further defined the theoretical basis for the method.[6] For a description in non-technical terms, there is a readable review by Matthews.[5]

We applied the methodology of extreme value theory to postoperative breathing patterns.

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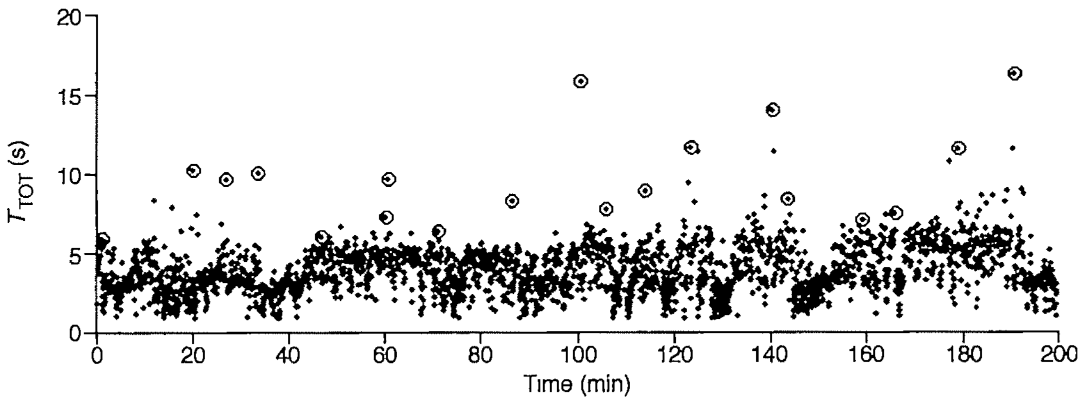

Fig 1 A typical time-series of breath times (T_{TOT}) for one patient (The $T_{TOT\ max}$ breaths for each 10-min period are circled.)

Methods

Clinical data collection

We used extreme value theory[7] to analyse data from an observational study of postoperative breathing patterns. Ethics committee approval and written consent had been obtained. Respiratory waveforms were monitored in 49 adult patients (31 male, mean (range) age 63 (range 21–82) yr), for a 3–4 h period starting 3–6 h postoperatively, once their breathing had stabilized, using an inductance plethysmograph (Respitrace, Studely Data Systems, Oxford, UK). All patients received supplemental oxygen and were monitored with continuous pulse-oximetry. Data were sampled at 20 Hz, converted with a 14-bit analogue-to-digital interface, and analysed using purpose written software which determined the T_{TOT} (time between successive breaths). This program marked each breath by detecting expiration–inspiration flow reversal. The signal was calibrated at the start of each session by the patient breathing to empty and fill 800-ml calibration bags. Breaths of less than 50 ml were ignored. We recognized that this could miss shallow breaths, but a threshold was necessary to reduce artifact from movement or cardiac pulsations. A single inductance band at the level of the nipple was used. We did not detect airflow at the mouth, and thus could not reliably differentiate obstructive and central apoeas.

The T_{TOT} data were divided into 10-min epochs. The longest T_{TOT} ($T_{TOT\ max}$) from each epoch (see Fig. 1) was used to produce a distribution of maxima, which was then subject to statistical analysis. This series of maxima can be thought of as analogous to the maximum annual height of floodwaters. The choice of 10 min for each epoch was arbitrary. It allowed a reasonable balance between having too few points to derive accurate estimates of the parameters of the extreme value distribution, and distorting the parameters by including too many data points that lay in the centre and not in the tail of the breath-time distribution. As we are interested in the long 'outlier' breaths, collecting more data of short breath-times does not improve our estimation of the probability of occurrence of apnoeas. We repeated the analysis using 1-min epochs without substantially different results.

Each patient was constantly observed throughout the study period by the investigator. Recordings were taken every 15 min for pain score, oxygen saturation, and level of sedation (using a simple linear scale:[7] sedation: 0='active', 1='quiet but eyes open', 2='rouse to voice', 3='rouse to glabellar tap', 4='unrousable').

Statistical modelling

A time series is said to be 'stationary' if the probability laws governing the process that is producing the series do not change during the duration of the series—the process is in statistical equilibrium. After manually checking the raw Respitrace signal for artifacts around any unusually long T_{TOT}, the stationarity of the series of T_{TOT} was checked by comparing the sample means and variances for the first and last half of each series. No non-stationarity was detected. Differences between the three groups were compared using either the chi-squared test for categorical data or the *t*-test for continuous data. The Mann–Whitney *U* test was used if the data distribution was skewed. A $P<0.05$ was considered significant. All data were analysed using the Matlab suite of mathematical functions (Matlab 5.3, The Mathworks Inc., Natick, MA, USA).

The distribution of T_{TOT} maxima was studied by using the Gumbel probability plot (see Appendix for Matlab Code). This plot is conceptually similar to the well-known normal probability plot. Each value from the series of (n) T_{TOT} maxima is ranked (i), and then plotted against its 'reduced value' ($y_i{:}n$). This reduced value is the double negative $\log_e$ expression of the datum rank—which is the distribution function for a type I distribution. It is given as follows:

$$y_i{:}n=-\log_e[-\log_e(p_i{:}n)] \quad \text{where } p_i{:}n=(i-0.5)/n.$$

If the plot was well-fitted by a straight line (see Fig. 2A), the extreme value distribution was termed 'standard'. If it

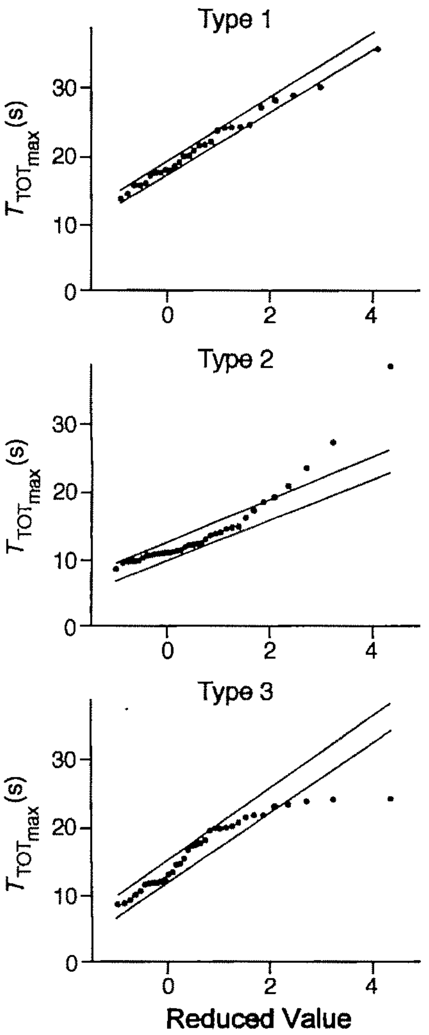

Fig 2 Gumbel plots. (A) 'Standard' (Gumbel distribution), (B) 'extended' (Frechet distribution), (C) 'finite' (Weibull distribution). The dashed lines indicate 95% confidence limits for a straight line (least-squares fit to all except the last 4 data points).

curved upwards it was termed 'extended', and if it curved down it was termed 'finite'. The T_{TOT} extreme probability distributions were thus classified according to whether the tail of the reduced-value plot deviated significantly and systematically outside the 95% confidence intervals (see Fig. 2) of a linear regression ($T_{\mathrm{TOT\ max}}=a+b\times y_{i:n}$); as fitted using least-squares to the linear Gumbel plot. Because the direction of the 'tail' of the plot was the object of interest the regression was done excluding the last four data points. In many cases the curves were obvious, and involved many more points than the last four (see Fig. 2). From the form of the distribution and knowledge of the parameter estimates, it is possible to infer the probability of apnoeas.

As shown in Figure 2C, the 'finite' distribution asymptotically approaches a finite upper limit. As a second analytic step, we therefore fitted a wash-in exponential function to the reduced-value data to predict the longest apnoea (using an iterative non-linear fitting procedure (Matlab: nonlinfit.m)).

Table 1 Summary of operation type, opioid type and route of administration—grouped according to type of extreme value breathing pattern. †P=0.05, chi-squared test. *P=0.15, chi-squared test, 'finite' *vs* 'standard' and 'extended' The morphine equivalent dose was calculated assuming fentanyl 200 μg = pethidine 100 mg = morphine 10 mg. No alteration for epidural *vs* parenteral potency was made

	Extreme value distribution type		
	Standard	**Extended**	**Finite**
Operation type			
Thoracic	5	3	11
Abdominal	5	3	10
Body surface	3	0	9
Opioid type†			
Pethidine	4	5	9
Morphine	3	1	15
Fentanyl	6	0	6
Route of administration *			
Parenteral	5	1	17
Epidural	8	5	13
Mean morphine equivalent dose (mg h^{-1}) (SD)	1.73 (1.05)	1.54 (1.27)	1.73 (1.83)
Mean T_{TOT} (s) (SD)	4.17 (0.96)	4.52 (0.84)	4.35 (1.27)
Mean of SD of T_{TOT} (s) (SD)	1.33 (0.46)	1.62 (0.42)	1.41 (0.95)

Results

We analysed more than 2000 breaths per patient. An example of a typical T_{TOT} series is shown in Figure 1. A summary of patient data is shown in Table 1.

When the T_{TOT} maxima were plotted, all three types of Gumbel plot were demonstrated in the study patients. Thirty patients (61.2%) fitted a 'finite' curve, which has a finite upper endpoint. This suggests that—depending on the value of the upper limit—we can have some confidence that an apnoea greater than a certain limit will never occur. Twenty-one patients (42%) had predicted worst apnoeas of less than 60 s.

Although not reaching statistical significance, a greater proportion of the patients who had epidural opioids (13 of 26 *vs* 6 of 23: P=0.15) had 'standard' or 'extended' plots. This result is confounded by the fact that these patients had more serious surgery. Conversely, more patients receiving i.v. morphine had 'finite' patterns (P=0.05), perhaps because i.v. morphine was given to patients after body-surface surgery.

There was no statistically significant relationship between the extreme value pattern and the mean and standard deviation of the T_{TOT} (Table 1). This suggests that often the shape of the tail of the T_{TOT} frequency distribution is relatively independent of the location and spread of the body of the T_{TOT} distribution. Patients in the group that displayed the 'finite' pattern were significantly less drowsy (mean (SD) drowsiness score 1.04 (0.92) *vs* 1.62 (0.62); P=0.03), suggesting that respiratory irregularity is related to the level of consciousness.

Discussion

In this preliminary study we have shown that extreme value theory can be applied to postoperative ventilatory patterns, and found all three different patterns. The 'finite' pattern has a definite ceiling value—the patient is statistically unlikely to have an apnoea that exceeds this value. The other two patterns have no defined maximum value.

Operation type, opioid dose, type, and route of administration did not strongly predict which pattern the patient would display. Less sedated patients were more likely to have a 'finite' pattern. The observational study design, and small numbers of patients, do not allow various confounding factors to be separated, and further work is required. It may be that a combination of mean T_{TOT} measurements (or ventilatory frequency), and statistical extreme value pattern, could allow apnoea prediction. With a more robust method of detecting respiration, the statistical methods could be automated and applied to large series of patients. In most cases the Gumbel plot curves are quite obvious, so shorter data series could be used with reasonable accuracy.

We made our observations once breathing patterns were stable. It would be necessary to determine whether the type of pattern that a patient displays reflects an individual response to opioids; or whether this is a dose–response relationship that changes with time. Perhaps the pattern could change following a dose of opioid, and the 'finite' pattern may be lost if the opioid dose is changed.

We could not differentiate obstructive from central apnoeas. Most of the apnoeas were probably central. Each patient was continuously observed by an investigator for the whole study period, and clinically detectable airway obstruction was uncommon. The distribution of T_{TOT} did not show multiples of the underlying ventilatory frequency. We may have missed some output from the respiratory centre during 'apnoea', because small breaths did not reach the 50-ml threshold required to qualify as a true breath. True monitoring of the respiratory centre output would require a monitor of muscle or nerve activity. We chose 50 ml as the threshold as a compromise between missing true breaths (false negatives) and including cardiac pulsations (false positives). When we used 30 ml as the cut-off, the mean respiratory rate approximated 1 Hz, which probably reflected cardiac motion. If we used thresholds greater than 50 ml there was minimal change in the calculated mean breathing rate as a function of threshold tidal volume. In practical terms, a tidal volume of 50 ml in a spontaneously breathing patient is unlikely to be functionally effective in gas exchange.

```
function y=gumbel(x),
% Input Series of TTOT(secs)is variable 'x'
% Outputs a graph of the Gumbel plot
% y are the 'reduced values'

%(1)Find TTOT maxima for 10min intervals
cs=cumsum(x),
interv=600;                %600sec=10min
seg=0,                     %counter for length of each epoch
kk=1,
oldseg=1,
for jj=1:length(cs),       %loop through series
    seg=seg+x(jj),
    s(jj)=seg,
    if seg>=interv;
       iseg=jj;            %captures the jj's at end of each epoch
       [maxx(kk),ix(kk)]=max(x(oldseg:iseg)),
       maxi(kk)=oldseg+ix(kk);   %ie maxima at time maxi, size maxx
       oldseg=iseg,
       seg=0,
       kk=kk+1,
    end
end
kk=kk-1;

%--------------------------------------------------------------
%(2)Calculate reduced values and do Gumbel plot from TTOT max data

nn=length(maxx),
[y,i]=sort(maxx),
pii(i)=(i-0.5)/nn;
y(i)=-log(log(pii)),               % reduced values
figure(1);plot(y,maxx,'r ');
xlabel('Reduced Value'),ylabel(' Ttotmax (sec)');
return,x
```

Fig 3 Matlab function to produce a Gumbel plot.

We conclude that extreme value methods can be used to study long breath-times in postoperative patients. Further work is needed to establish whether this method might become a useful routine postoperative monitoring tool to identify patients at risk of respiratory depression.

Appendix

Matlab Code to produce a Gumbel plot is shown in Figure 3.

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Randomized controlled trial to investigate influence of the fluid challenge on duration of hospital stay and perioperative morbidity in patients with hip fractures[†]

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Background. A prospective, randomized controlled trial comparing conventional intraoperative fluid management with two differing methods of invasive haemodynamic monitoring to optimize intraoperative fluid therapy, in patients undergoing proximal femoral fracture repair under general anaesthesia.

Methods. Ninety patients randomized to three groups; conventional intraoperative fluid management (Gp CON, n=29), and two groups receiving additional repeated colloid fluid challenges guided by central venous pressure (Gp CVP, n=31) or oesophageal Doppler ultrasonography (Gp DOP, n=30). Primary outcome measures were time to medical fitness to discharge, hospital stay and postoperative morbidity.

Results. The fluid challenge resulted in significantly greater perioperative changes in central venous pressure between Gp CVP and Gp CON (mean 5 (95% confidence interval 3–7) mm Hg) (P<0.0001). Important perioperative changes were also shown in Gp DOP with increases of 49.4 ms (19.7–79.1 ms) in the corrected flow time, 13.5 ml (7.4–19.6 ml) in stroke volume, and 0.9 (0.49–1.39) litre min^{-1} in cardiac output. As a result, fewer patients in Gp CVP and Gp DOP experienced severe intraoperative hypotension (Gp CON 28% (8/29), Gp CVP 9% (3/31), Gp DOP 7% (2/30), P=0.048 (chi-squared, 2 degrees of freedom (df)). No differences were seen between the three groups when major morbidity and mortality were combined, P=0.24 (chi-squared, 2 df). Postoperative recovery for survivors, as defined by time to be deemed medically fit for discharge, was significantly faster, in comparison with Gp CON, in both the Gp CVP (10 *vs* 14 (95% confidence interval 8–12 *vs* 12–17) days, P=0.008 (t-test)), and Gp DOP (8 *vs* 14 (95% confidence interval 6–12 *vs* 12–17) days, P=0.023 (t-test). There were no significant differences between groups, for survivors, with respect to acute orthopaedic hospital and total hospital stay.

Conclusions. Invasive intraoperative haemodynamic monitoring with fluid challenges during repair of femoral fracture under general anaesthetic shortens time to being medically fit for discharge.

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Keywords: surgery, femoral fracture; measurement techniques, oesophageal Doppler ultrasonagraphy; complications, postoperative hypotension; monitoring, intraoperative

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Hip fracture patients are an elderly hospital population who are at high risk of postoperative complications and mortality, and consequently represent an important resource allocation. They occupy 20% of orthopaedic beds, for an average of 25.1 days, with a variable 90-day mortality of between 5 and 24%,[1 2] and less than a quarter of survivors return to their pre-fracture activities of daily living at 90 days.[1 2] In our hospital, patients at high risk of postoperative morbidity and mortality presenting for major surgery, are admitted to the intensive care/high dependency unit for optimization of cardiac output and tissue oxygen delivery, with the aid of a pulmonary artery catheter, as suggested by Boyd and colleagues.[3] This has resulted in a 75% reduction in mortality and 50% reduction in major morbidity, and these improvements have been sustained in our hospital.[4] Unfortunately, the National Health Service does not have the resources at present to admit all patients presenting with hip fracture to a critical care area as has been suggested,[5] and pulmonary artery catheterization is not easily performed outside the theatre or critical care setting.

An alternative solution was, therefore, needed to optimally manage this high-risk hip fracture population, since an audit of 94 consecutive hip fractures in our hospital had shown that increased intraoperative fluid administration was associated with decreased morbidity and mortality. Sinclair and colleagues[6] showed that intraoperative volume optimization guided by oesophageal Doppler ultrasonography led to reductions in postoperative recovery and hospital stay in patients with fractured hips. Doppler ultrasonography is not easily available in all hospitals and requires a degree of operator skill with the patient deeply sedated or anaesthetized to tolerate the insertion of the ultrasound probe into the oesophagus. Central venous pressure measurement is, however, routinely used for haemodynamic monitoring and treatment during major operations, and has the advantage that it is well tolerated by an awake patient. Consequently we investigated whether repeated colloid fluid challenges to optimize the circulation intraoperatively, guided by central venous pressure or oesophageal Doppler ultrasonography, would benefit high-risk patients admitted with fractured hips to a London teaching hospital.

Methods

Following approval of the Local Research Ethics Committee (LREC 98.15.18), all patients admitted with fractured hips were considered for inclusion into this study. Informed written consent was sought from all patients, but was not possible for 35 patients because of diminished mental capacity. Patients who were unable to give informed consent themselves were not excluded, but the next of kin was informed where possible, in accordance with the LREC guidelines. Exclusion criteria were patients aged less than 65 yrs, oesophageal pathology, patients with a central venous cannula already *in situ*, pathological fracture of femur, refusal of informed consent, and patients undergoing regional anaesthesia.

Preoperatively patients received any necessary medical interventions felt appropriate by the admitting orthopaedic surgeons, and all patients received regular oral paracetamol and dihydrocodeine, and i.m. morphine as required for analgesia. Maintenance i.v. fluid (1000 ml crystalloid 12 hourly) was commenced from the time that the patient was scheduled to undergo surgery and continued up to the time of operation. Mobility before fracture and mental test score[7] were recorded. Severity of illness was recorded using the American Society of Anesthesiologists' grading of Health Status,[8] and by calculation of the physiology and operative severity score for the enumeration of mortality and morbidity (POSSUM) for the orthopaedic population.[9]

The conduct of general anaesthesia performed for all patients was standardized and managed by an independent clinician. The investigator team initiated the additional fluid-directed therapy. Induction of anaesthesia consisted of propofol and fentanyl, intubation was facilitated by vecuronium, and anaesthesia was maintained with oxygen, nitrous oxide, and isoflurane. No specific premedication was used although some patients received i.m. opiates before surgery for analgesia. Perioperative analgesia was provided for by a combination of fentanyl, nitrous oxide and a '3 in 1' inguinal perivascular nerve block.[10] Where peripheral nerve block was not possible or considered contraindicated, i.v. morphine was administered to provide immediate postoperative analgesia. Essential monitoring of the cardiovascular and respiratory systems was commenced before induction and continued into the recovery period as per routine practice.

In addition, patients were individually randomized into three groups, through the use of a set of computer-generated random numbers and an opaque sealed envelope technique, to receive further minimally invasive haemodynamic monitoring. The control group (Gp CON) and central venous pressure-directed therapy group (Gp CVP) received a catheter inserted into a central vein (Angiocath 16 G, Becton Dickinson, UT, USA), or Drum-cartridge catheter 16 G (Abbott, Ireland) for the basilic/cephalic vein approach. The Doppler-directed therapy group (Gp DOP) received a 6-mm diameter oesophageal Doppler (OD) ultrasound probe (Deltex Medical Ltd, Chichester, UK) inserted through the mouth into the oesophagus, after induction of anaesthesia. The central venous catheter was connected to a pressure transducer, and the pressure trace displayed continuously and recorded every 10 min. The OD probe was connected to the ultrasound source and detector and continuously monitored. After positioning in the oesophagus as previously described,[6] the OD probe measured and displayed cardiac output, stroke volume, and corrected aortic systolic flow time continuously and these results were recorded every 10 min.

Intraoperatively, all patients received i.v. crystalloid (Hartmann's solution), colloid in the form of gelofusine,

Time	**CVP (mm Hg)**	**Gelofusine fluid challenge**
Initial reading	<14	200 ml
	≥14	100 ml
During fluid challenge	Increase >5	Stop fluid challenge and WAIT
Following fluid challenge	Increase >3	WAIT
	≤3	Repeat fluid challenge as per initial reading

Fig 1 Procedure to guide gelofusine fluid challenges according to dynamic changes in central venous pressure, for CVP-directed therapy group (Gp CVP).

or blood to replace estimated and measured fluid losses, in an attempt to maintain heart rate and arterial pressure within 20% of pre-induction baseline levels. In Gp CON, clinicians were able to give i.v. fluid as they thought appropriate. Although central venous pressure was monitored and recorded by the investigator, the clinician was unaware of these measurements and so was unable to use them to guide therapy. The investigator gave no additional fluids in this group. In Gp CVP, patients received additional 200 ml gelofusine fluid challenges guided by the response of the central venous pressure to a fluid challenge from the investigator, in addition to any fluid given by the clinician. This procedure was formulated by modifying guidelines produced by Weil and colleagues,[11] and is shown in Figure 1. In Gp DOP, patients received additional 200 ml gelofusine fluid challenges guided by Doppler measurements of stroke volume and corrected flow time from the investigator, in addition to any fluid given by the clinician. This procedure was similar to that performed by Sinclair and colleagues,[6] with the exception that if the corrected flow time rose above 0.4 s and the stroke volume remained the same, a further 100 ml gelofusine fluid challenge was given. If after this fluid challenge the stroke volume still remained the same then no further fluid was given until the stroke volume fell by 10%. The rationale for this minor change was based on observations in similar age group patients before the study, where the initial corrected flow time was frequently greater than 0.4 s although these patients were obviously clinically hypovolaemic and responded appropriately to a fluid challenge.

Operation time was recorded as being the time from when the patient entered the operating theatre to the time of skin closure. The 'initial' and 'final' recordings of central venous pressure or oesophageal Doppler ultrasonography measurements were at the start and end of the operating time. The anaesthetist was unaware of the central venous pressure or oesophageal Doppler ultrasonography measurements, by the use of stand-alone monitors, which were screened from the anaesthetist. The anaesthetist was, however, informed of all fluid volumes given in the procedure groups (Gp CVP and Gp DOP). At the end of the operation, the central venous cannula or OD probe was removed from the patient. Severe intraoperative hypotension was defined as greater than 50% reduction in systolic arterial pressure requiring rapid fluid infusion by the anaesthetist and/or vasoconstrictor therapy.

Postoperative management was performed by the orthopaedic medical team and nursing staff who were all unaware of the patient's randomization. Major postoperative morbidity for survivors was recorded as used in the data collection for the POSSUM scoring system.[9] The dates of discharge or transfer from the orthopaedic ward were recorded to determine duration of acute orthopaedic hospital stay and total hospital stay, which included acute orthopaedic and geriatric care, for survivors. However, it is well recognized that in elderly orthopaedic patients the duration of hospital stay is often related to social circumstances and not to clinical health.[12] Consequently, the time when these patients were deemed medically fit by the orthopaedic team to return to their previous abode was also documented.

Statistical analysis

Primary outcome measures were time to medical fitness to discharge, hospital stay, and postoperative morbidity in survivors. Secondary outcome measures were differences in intraoperative central venous pressure measurements between Gp CON and Gp CVP, and severe intraoperative hypotension between all three groups.

From previous studies and our own audit, the sample size (30 in each group) was determined to show a one-fifth reduction in time to medical fitness to discharge,[6] and hospital stay,[6] and a 50% reduction in the total number of postoperative complications for survivors in Gp CVP and Gp DOP[3 13] (α value of 0.05, and a β value of 0.8). The control group (Gp CON) stay was based on our previous audit and was comparable with that of Sinclair and colleagues.[6] ANOVA and the t-test were used for continuous data. The chi-squared test with 2 degrees of freedom (df) was used to compare categorical variables between the three groups. For comparing number of days to discharge, the reciprocal value was used in order to normalize the distribution. Confidence intervals are shown after back transforming. Mean and 95% confidence intervals are quoted unless otherwise stated. P value <0.05 was considered significant.

All analysis was carried out using Statview for Windows software package (version 4.57; Abacus Concepts Inc, Berkeley, CA, USA).

Results

One hundred and fourteen patients were visited preoperatively of whom 90 met the entry criteria. Randomization resulted in 29 patients allocated to Gp CON, 31 to Gp CVP, and 30 to Gp DOP. The operation was changed for one

Table 1 Physical characteristics of patients, preoperative and operative characteristics in the control group (Gp CON), CVP-directed therapy group (Gp CVP), and Doppler-directed therapy group (Gp DOP). Values are mean (SD), median (interquartile range), or numbers of patients. Significantly greater number of DHS procedures performed in Gp CVP compared with Gp CON (*P*=0.04) and Gp DOP (*P*=0.05)

	Gp CON	Gp CVP	Gp DOP
Number allocated	29	31	30
Age (yr) [range]	84.5 (9.3) [65–102]	85.0 (6.2) [74–98]	82.0 (8.7) [65–97]
Sex (M.F)	6.23	4.27	6.24
American Society of Anesthesiologists' grading	3 (3–4)	3 (3–4)	3 (2.5–3)
POSSUM (orthopaedic)	38 (34–40)	40 (35–42)	35 (32–40)
Predicted mortality from POSSUM (%)	15.3 (9.4–19)	19 (10.9–26.3)	11.6 (7.7–19)
Mental test score	10 (5–10)	8 (3.5–10)	7.5 (2–10)
Mobility before fracture			
Fully mobile	18	13	20
Requires aid (e.g. stick) or transfers only	11	18	10
Operative delay (days)	2 (1–2)	2 (1–2)	2 (1–2.5)
Preoperative intravenous fluids (litres 24 h^{-1})	2 (1–2)	1.5 (1–2)	1.25 (0.5–2)
Operation			
Dynamic hip screw	11	21	13
Arthroplasty	17	9	14
AO screw	1	0	3
Operative time (min)	70 (55–80)	70 (42.5–80)	57.5 (47.5–65)
'3 in 1' nerve block	16	20	20

Table 2 Intraoperative fluids and blood loss in the control group (Gp CON), CVP-directed therapy group (Gp CVP), and Doppler-directed therapy group (Gp DOP). Values are means (95% confidence intervals)

	Group A (control)	Group B (CVP)	Group C (Doppler)	ANOVA *P* value
Intraoperative crystalloid (ml)	1286 (1100–1473)	1156 (998–1315)	1120 (983–1257)	0.31
Intraoperative colloid (ml)	448 (319–576)	1123 (921–1324)	1207 (1077–1336)	<0.0001
Intraoperative blood loss (ml)	341 (263–420)	429 (299–560)	275 (215–336)	0.07
Total intraoperative fluids minus blood loss (ml)	1392 (1170–1615)	1850 (1654–2045)	2051 (1854–2249)	<0.0001

patient in Gp CVP, following randomization, to intramedullary femoral nailing, but data are included on an intent to treat basis. The physical characterization of patient's severity of illness, preoperative mobility, mental test score, preoperative delay to operation, preoperative fluids, operative time, and number of patients receiving a nerve block were similar in the three groups (Table 1). Patients underwent significantly more dynamic hip screw procedures in Gp CVP compared with Gp CON (*P*=0.04) and Gp DOP (*P*=0.05).

There were no complications related to oesophageal Doppler ultrasonography, but central venous cannula insertion resulted in one pneumothorax (resolved spontaneously with no intervention) and four carotid artery punctures (resulted in minor bruising only).

Patients in the two procedure groups (Gp CVP and Gp DOP) had a significantly greater positive fluid balance intraoperatively (457 (137–777) and 659 (336–982) ml, respectively) than Gp CON, *P*<0.0001 (ANOVA) (Table 2). Perioperative changes seen in Gp DOP were increased corrected flow time 49.4 ms (19.7–79.1 ms), increased stroke volume 13.5 ml (7.4–19.6 ml), and increased cardiac output 0.9 litre min^{-1} (0.49–1.39 litre min^{-1}). There was a significantly greater increase in central venous pressure in Gp CVP compared with Gp CON (mean 5 (95% confidence interval 3–7) mm Hg) (*P*<0.0001) (Fig. 2).

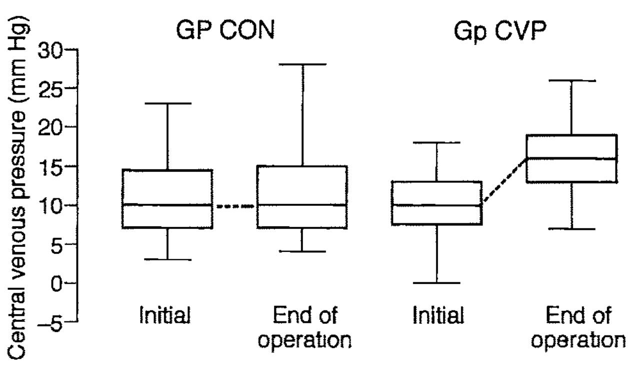

Fig 2 Changes in intraoperative central venous pressure measurements between the control group (Gp CON) and CVP-directed therapy group (Gp CVP) (Median, interquartile range and extremes shown)

Severe intraoperative hypotension was recorded in eight, three, and two patients in Gp CON, Gp CVP, and Gp DOP respectively, *P*=0.048 (chi-squared, 2 df). This reduction in patients with intraoperative hypotension was not statistically significant between Gp CVP and Gp CON (*P*=0.07), in contrast to Gp DOP *vs* Gp CON (*P*=0.03). Postoperative morbidity for survivors in Gp CVP and Gp DOP was seen in 8/31 (26%) and 7/30 (23%) patients, respectively, compared with 14/29 (49%) patients in the control group, *P*=0.078 (Table 3). Overall predicted morbidity from POSSUM was

59%. There were a total of 11 hospital deaths during the course of the study, two in Gp CON, six in Gp CVP, and three in Gp DOP (*P*=0.31). No differences were seen between the three groups when major morbidity and mortality were combined, *P*=0.24. Overall predicted mortality from POSSUM was 18%, and actual mortality 12%. The median POSSUM scores for those who died were high (47.5) predicting a high mortality in this group (predicted POSSUM mortality=72%).

There was a statistically significant reduction in the number of days to being declared medically fit for discharge, for survivors, between the three groups, Gp CON 14 (12–17) days, Gp CVP 10 (8–12) days and Gp DOP 8 (6–12) days, *P*=0.035 (ANOVA) (Table 4). This reduction in days was significant when comparing both the Gp CVP and Gp CON (10 *vs* 14 (95% confidence interval 8–12 vs 12–17), respectively) days, *P*=0.008 (*t*-test)), and Gp DOP and Gp CON (8 *vs* 14 (95% confidence interval 6–12 *vs* 12–17), respectively) days, *P*=0.023 (*t*-test). There were no significant differences between the three groups, for survivors, with respect to acute orthopaedic hospital stay and total hospital stay, *P*=0.20 and 0.30, respectively (ANOVA). Total number of hospital days (survivors and non-survivors) between the three groups are shown in Figure 3.

Table 3 Episodes of postoperative morbidity (in survivors) in the control group (Gp CON), CVP-directed therapy group (Gp CVP), and Doppler-directed therapy group (Gp DOP) Total episodes of morbidity in survivors shown, followed by total episodes of morbidity and mortality in all patients *Postoperative day 8

Description of postoperative morbidity[9]	**Numbers of patients**		
	Gp CON	**Gp CVP**	**Gp DOP**
Deep haemorrhage requiring >2 unit blood transfusion	1	0	1
Haematemesis	1	0	0
Chest infection	5	3	2
Wound infection	2	0	0
Urinary tract infection	3	1	2
Cellulitis	0	1	0
Pancreatitis	1	0	0
Pulmonary embolus	0	0	1
Cerebrovascular accident	1	1	2
Myocardial infarction	0	1	0
Cardiac failure	0	1*	0
Rapid atrial fibrillation	2	1	3
Hypotension	3	0	0
Impaired renal function	2	0	0
Pseudo-obstruction	0	1	0
Total morbidity in survivors	*21*	*10*	*11*
Mortality	2	6	3
Total morbidity and mortality	*23*	*16*	*14*

Discussion

Patients presenting to our hospital with hip fractures are an elderly population (median age 85 yrs), who are at high risk of perioperative morbidity and mortality as illustrated by their POSSUM scores. They are frequently hypovolaemic on admission to hospital for a variety of factors including concomitant therapies (e.g. diuretics), inadequate fluid intake because of immobility following fracture and/or dementia, and reluctance to drink because of anxiety over incontinence. This will exacerbate any tissue hypoperfusion arising as a result of surgery with potential organ dysfunction in the perioperative period. This may be reflected clinically in increased postoperative morbidity, duration of hospital stay and mortality. Perioperative optimization of the circulatory volume aims to maximize cardiac performance and thus minimize this tissue oxygen debt in the perioperative period.[3 6 14 15] The significantly increased intraoperative fluid administration in the two procedure-driven groups (Gp CVP and Gp DOP) in this study was a consequence of this concept, and translated into clinical benefits. We showed a reduction in the frequency of intraoperative hypotension, a trend towards reduced postoperative morbidity in survivors and a faster postoperative recovery, gauged by the reduction in the number of days before being declared medically fit for discharge from hospital compared with the control group. There is frequent anxiety amongst clinicians in the perioperative period that these elderly groups of patients with comorbidities are at danger of i.v. fluid overload, which may potentially lead to cardiac failure, and thus there is a reluctance to prescribe sufficient i.v. fluids. In this study we have clearly shown that the majority of patients in fact have occult hypovolaemia, and tolerate increased i.v. fluid therapy to their benefit.

It is well recognized that routine perioperative haemodynamic monitoring (heart rate and arterial pressure) is insensitive to occult hypovolaemia,[14] and is only able to detect major circulatory losses. Consequently, invasive methods of monitoring the circulation will be required if occult hypovolaemia is to be adequately treated and inadvertent fluid overload avoided. The wide range of additional colloid required in our procedure groups (Gp CVP and Gp DOP) emphasizes the fact that giving a single volume load is not appropriate when applied to individuals. Fluid must be individually titrated to dynamic changes in

Table 4 Days before declared medically fit for discharge, acute orthopaedic and total (orthopaedic and geriatric) hospital stays for survivors, in the control group (Gp CON), CVP-directed therapy group (Gp CVP), and Doppler-directed therapy group (Gp DOP) Values are means (95% confidence intervals)

	Gp CON	**Gp CVP**	**Gp DOP**	ANOVA ***P* value**
Days before declared medically fit for discharge	13.9 (11.9–16.9)	10.0 (8.1–12.0)	7.7 (5.9–12.3)	0.035
Acute orthopaedic hospital stay (days)	16.7 (13.2–22.2)	11.1 (8.3–17.5)	12.5 (11.1–16.7)	0.17
Total (orthopaedic and geriatric) hospital stay (days)	17.5 (13.9–24.4)	13.3 (10.3–19.2)	13.5 (10.9–17.5)	0.27

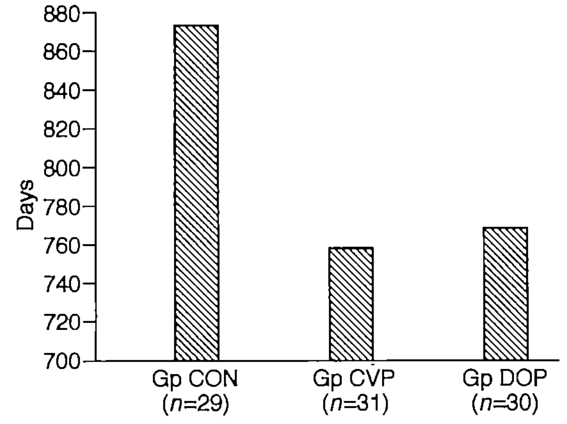

Fig 3 Total number of days spent in hospital (orthopaedic and geriatric), for all study patients (survivors and non-survivors), between the control group (Gp CON), CVP-directed therapy group (Gp CVP), and Doppler-directed therapy group (Gp DOP)

appropriate monitoring. The effectiveness of oesophageal Doppler ultrasonography has already been proven in this context,[6] and our study confirms this. Unfortunately, the present lack of familiarity and availability of this monitor, combined with the necessity for a sedated patient for insertion and manipulation of the OD probe, have so far prevented its widespread introduction for perioperative use. We have shown that monitoring the dynamic changes of central venous pressure in response to a fluid challenge produces equivalent benefits. The advantage of both techniques is that they do not require a critical care bed.

Several factors are known to influence outcome in this particular population of patients including dementia, reduced pre-fracture mobility and operative delay.[16–18] There were no differences in these three factors between the groups studied. General anaesthesia has no adverse effect on outcome for fracture hip repair although one study showed reduced early mortality for subarachnoid anaesthesia.[19] However, there were no differences in mortality rates at 2 months and both the Cochrane review[20] and The Baltimore Hip Studies group[21] have failed to show any benefit from subarachnoid anaesthesia. The early reduction in mortality with subarachnoid anaesthesia may simply be a reflection of increased fluid loading given to counteract the sympathetic block, which coupled with the consequent vasodilatation will reduce tissue hypoperfusion and protect against thromboembolism. Although a significantly greater number of DHS procedures occurred in Gp CVP, no differences in morbidity and mortality have previously been shown between DHS and hemiarthroplasty.[22]

There was no statistical difference in mortality between the groups and the study was purposefully not powered to show any difference in mortality. This would have required over 300 patients. It was felt unlikely that we would improve medium and long-term mortality, which are determined by the co-morbidities frequently precipitating the fall and subsequent fracture, such as dementia and reduced mobility as a result of a variety of pathologies.

We were unable to show an actual reduction in acute orthopaedic or total hospital stay. Duration of hospital stay is often a poor indicator of outcome because it depends on too many variables.[12] In the elderly hip fracture population, this is even more evident as arrangements for assessments of daily living activity and institution of subsequent recommendations varying from home adaptions to organization of nursing home care, take time to organize, and are usually a scarce resource. Consequently, our collection of the data recording duration to being declared medically fit for discharge is more meaningful as a medical outcome measure. That the patient subsequently stayed in hospital longer than this period is an indication of the complexity of arranging discharge from hospital for these elderly patients. Sinclair and colleagues,[6] showed reductions in hospital stay in addition to medical fitness to discharge and this may have been a reflection of their younger and fitter population. It is unlikely that a single intraoperative intervention will ever show the economic benefit of a reduction in hospital stay in our hip fracture population, because of the complexity of discharge for these patients. However if included in a package of care which addresses all those other factors which are known to affect outcome in the hip fracture population,[16] then this intervention may impact on hospital stay with subsequent socio-economic benefits.

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Double-blind, placebo-controlled analgesic study of ibuprofen or rofecoxib in combination with paracetamol for tonsillectomy in children

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Background. The analgesics used for paediatric tonsillectomy may be associated with side-effects such as sedation, respiratory depression and vomiting (opioids) or increased bleeding [non-steroidal anti-inflammatory drugs (NSAIDs)]. In our institution, we employ a combination of paracetamol, NSAID and opioid, although there is no published evidence of analgesic benefit from adding NSAIDs to paracetamol in children.

Methods. This randomized, double-blinded clinical study examined the analgesic effectiveness of combining paracetamol (20 mg kg^{-1}) with rofecoxib (0.625 mg kg^{-1}), ibuprofen (5 mg kg^{-1}) or placebo as premedication for (adeno)tonsillectomy (n=98) in children aged 3–15 yr. Intravenous fentanyl 1–2 μg kg^{-1} was given intraoperatively. Regular oral paracetamol (15 mg kg^{-1}, 4 hourly) was given after operation and could be supplemented on request from the child with oral ibuprofen 5 mg kg^{-1} or oral codeine 1 mg kg^{-1}. The primary outcome variable was need for early supplementary analgesia (within 2 h after surgery).

Results. The addition of ibuprofen to paracetamol reduced the need for early analgesia from 72% to 38% of children (difference 34%; 95% confidence interval 4–64%). The addition of rofecoxib to paracetamol did not significantly alter the need for early analgesia (68 *vs* 72%). Pain scores were higher in those children who required early analgesia. There were no differences between the groups in operative blood loss or complications, total 24-h analgesic consumption, pain scores at 4 and 8 h, vomiting or antiemetic use.

Conclusion. This study provides evidence to support the combination of ibuprofen (but not rofecoxib) with paracetamol for perioperative analgesia in children.

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Keywords: analgesics non-opioid, ibuprofen; analgesics non-opioid, paracetamol; analgesics non-opioid, rofecoxib; antagonists, cyclo-oxygenase type 2 antagonist; surgery, otolaryngological; surgery, paediatric

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Tonsillectomy is one of the most common surgical procedures in children, with an estimated yearly rate in the UK of 2.3/1000 for the population aged under 12 yr. Increasing attention is being paid to the control of perioperative pain in children with the development of validated pain scales and more vigorous employment of analgesic techniques.[1] However, the provision of adequate analgesia after tonsillectomy presents the clinician with difficulties as this is a painful procedure and it may be associated with significant bleeding into the airway. Opioids are frequently used and provide effective analgesia for tonsillectomy[2] but are associated with a high incidence of nausea and vomiting.[3] In addition, there are concerns about opioid-induced respiratory depression and sedation, which may make recovery hazardous after pharyngeal surgery,[4 5] particularly in children with a history of obstructive sleep apnoea. Non-steroidal anti-inflammatory drugs (NSAIDs) have a similar analgesic effect to opioids for tonsillectomy[5] and are opioid-sparing in the recovery period.[4] However, the perioperative use of NSAIDs has been limited because of concerns over increased postoperative bleeding, which has been demonstrated with ketorolac,[6 7] although apparently not for other NSAIDs.[8] Paracetamol has been shown to be an effective and relatively safe analgesic in children[9 10]

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and is often used to provide a background of analgesia after surgery, but appears to be insufficiently potent if used alone for tonsillectomy pain.[11]

The current practice in our unit is to use a balanced approach[12] with a combination of regular paracetamol and NSAIDs plus opioid as needed to provide perioperative analgesia for tonsillectomy.[13] However, there is no published evidence to support the use of NSAIDs with paracetamol for perioperative analgesia in children. A recent study of children after appendectomy failed to show any additional morphine-sparing effect from combining paracetamol with diclofenac.[14] This contrasts with an adult study, which showed the combination of paracetamol and diclofenac to reduce postoperative morphine consumption compared with either drug alone.[15]

The recently introduced cyclo-oxygenase type 2 (COX-2) inhibitors, such as rofecoxib,[16] may have advantages for analgesia in paediatric tonsillectomy. They have analgesic power equivalent to that of NSAIDs for dental extraction pain.[17 18] Their COX-2 selectivity produces minimal effect on platelet aggregation. In addition, rofecoxib has a syrup formulation, excellent oral bioavailability and a half-life of action of 17 h, allowing once-daily dosing. These properties potentially make it a good candidate for perioperative use in paediatrics to help reduce 'tears at bedtime'.[19] Currently, there are no pharmacokinetic or pharmacodynamic data on the use of COX-2 antagonists in children. Rofecoxib 50 mg has been shown to be equianalgesic to ibuprofen 400 mg in the adult dental pain model.[17] We have used this measure of the potency of rofecoxib to estimate an equianalgesic paediatric dose (0.625 mg kg^{-1}) as being one-eighth of the paediatric ibuprofen dose (5 mg kg^{-1}).

The aim of our randomized, double-blinded, placebo-controlled pragmatic clinical study was to examine whether combining a NSAID (ibuprofen 5 mg kg^{-1}) or COX-2 antagonist (rofecoxib 0.625 mg kg^{-1}) with paracetamol (20 mg kg^{-1}) before paediatric tonsillectomy would confer analgesic benefits without increasing intraoperative blood loss.

Methods

The study was approved by the hospital ethics committee. A Clinical Trials Exemption certificate was obtained from the Medicines Control Agency of the UK to allow the use of rofecoxib as an analgesic in children. After written informed parental consent and verbal child assent had been obtained, 103 children, ASA I or II, aged 3–15 yr, presenting for elective tonsillectomy or adenotonsillectomy, were entered in the trial. Using a computer-generated random number table, a hospital pharmacist allocated the children randomly to three groups: placebo, rofecoxib or ibuprofen. Both the patients and the investigators were blinded to the study group assignment. Exclusion criteria were sensitivity to NSAIDs, bleeding diathesis, renal or hepatic impairment and severe asthma (requiring recent hospital admission or oral corticosteroid therapy). On enrolment in the study, the children were familiarized with the Oucher visual analogue pain scale, which has been validated in children[20] and used previously to score tonsillectomy pain.[21]

The children were premedicated 1 h before surgery with paracetamol syrup 20 mg kg^{-1} and either placebo, ibuprofen 5 mg kg^{-1} or rofecoxib 0.625 mg kg^{-1} (syrups 0.25 ml kg^{-1} to a maximum of 10 ml). Therefore, the maximum dose was ibuprofen 200 mg or rofecoxib 25 mg. Induction of anaesthesia was with propofol or sevoflurane and the airway was secured with a reinforced laryngeal mask (53% of children) or endotracheal tube (47%). Atracurium 0.5 mg kg^{-1} was used to facilitate intubation. Anaesthesia was maintained with isoflurane in 33% oxygen/67% nitrous oxide and intraoperative analgesia was provided with fentanyl 1–2 $\mu g\ kg^{-1}$. No NSAIDs, paracetamol or prophylactic antiemetic were given in theatre. Intraoperative blood loss was assessed by weighing swabs (assuming 1 g=1 ml blood) and by measuring losses to calibrated suction bottles.

A standardized postoperative analgesic regimen was prescribed of regular paracetamol (15 mg kg^{-1}, 4 hourly) with oral ibuprofen (5 mg kg^{-1}) or oral codeine (1 mg kg^{-1}) to be administered at the child's request by the ward nursing staff. Pain was scored whenever supplementary analgesia was administered and also 4 and 8 h after premedication, when the the first two postoperative doses of paracetamol were given. Children were considered to have required early supplementary analgesia if they received either ibuprofen or codeine within 2 h after surgery. Children were discharged home the day after surgery.

The primary outcome variable was the need for early postoperative analgesia. Secondary outcome variables were intraoperative blood loss, time to first postoperative analgesia, Oucher pain scores, analgesic consumption in the first 24 h, vomiting, antiemetic use and incidence of primary and secondary haemorrhage. The data were collected by the anaesthetist, theatre and ward nurses and subsequently validated by review of the clinical notes.

Differences among groups were compared using the Kruskal–Wallis test for non-parametric data, one-way analysis of variance for parametric data and the χ^2 test or Fisher's exact test for nominal data. $P<0.05$ was considered significant. A sample size calculation based on audit data from our hospital showed that 60% of children premedicated with paracetamol and receiving rectal diclofenac intraoperatively required early postoperative analgesia Therefore, to show a 50% reduction in the need for early analgesia in the rofecoxib group, we estimated that 42 patients were required per group (power of 80% and $P<0.05$). To minimize the size of the placebo group, a blinded interim analysis was planned by the statistician at the halfway point. If this showed a greater need for early postoperative analgesia in the placebo group than the ibuprofen group, then recruitment to the placebo group would cease.

Table 1 Patient characteristics and intraoperative details Data are median (interquartile range) or mean (SD) There were no significant differences between the groups in any of the variables. T=tonsillectomy; T&A=tonsillectomy and adenoidectomy

	Drug group		
	Placebo (*n*=18)	**Rofecoxib (*n*=40)**	**Ibuprofen (*n*=40)**
Excluded (*n*)	1	2	2
Age (yr)	7.0 (5–9)	7.5 (5–11)	7.0 (5–11)
Weight (kg)	25 (20–31)	29 (21–49)	28 (21–42)
Sex (male:female)	7:11	16:24	21:19
Asthmatic (%)	4 (22%)	6 (15%)	2 (5%)
Time from premedication to surgery (min)	81 (33)	73 (28)	82 (28)
Operation type (T:T&A)	11:7	22:18	22:18
Operation duration (min)	20.1 (8.5)	21.0 (10.0)	21.2 (9.0)
Fentanyl dose (μg kg^{-1})	1.46 (0.6)	1.34 (0.4)	1.37 (0.4)

Table 2 Primary and secondary outcomes. Data are percentage (*n*) or median (interquartile range) 'Primary haemorrhage' indicates bleeding requiring intervention within 24 h, 'Secondary haemorrhage' indicates delayed bleeding requiring readmission

	Drug group			***P***
	Placebo	**Rofecoxib**	**Ibuprofen**	
Supplementary analgesic <2 h (*n*)	72% (13)	68% (27)	43% (17)	0.03
Time to supplementary analgesia (min)	62 (35–250)	62 (35–278)	156 (55–300)	0.09
Pain score at 4 h	20 (0–40)	20 (10–40)	20 (18–40)	0.89
Vomited (*n*)	22% (4)	33% (13)	28% (11)	0.71
Antiemetic administered (*n*)	22% (4)	20% (8)	20% (8)	0.97
Primary haemorrhage (*n*)	5.5% (1)	2.5% (1)	5% (2)	0.83
Secondary haemorrhage (*n*)	11% (2)	7.5% (3)	2.5% (1)	0.30

Results

Of the 103 children recruited, five were excluded because of protocol violations (two were too young and three received diclofenac in theatre). The patient and surgical characteristics were comparable across the groups (Table 1). There were no differences in the time from premedication to the start of surgery [78 (29) min; pooled mean (SD)], operation type (tonsillectomy or adenotonsillectomy), duration of surgery or dose of intraoperative fentanyl (Table 1).

The interim blinded analysis showed that more children in the placebo group received early postoperative analgesia than in the ibuprofen group (72 *vs* 38%; difference 34%, 95% confidence interval 4–64%). Therefore recruitment to the placebo group was stopped at 18 children. Significantly more children required early analgesia (within 2 h after surgery) in the rofecoxib group compared with the ibuprofen group (68 *vs* 43%; difference 25%, 95% confidence interval 4–46%) (Table 2). The pain scores at the time of administration of supplementary analgesia were significantly higher in those children requesting early analgesia (median 60 *vs* 40, $P<0.0001$). By the time of the first postoperative paracetamol dose, there was no difference in pain scores between the groups (Table 2). There was no difference between the groups in total analgesic consumption in the first 24 h, in the incidence of vomiting or the need for antiemetic (Table 2).

There was greater surgical blood loss in children having adenotonsillectomy than in those having tonsillectomy [median (interquartile range) 2.6 (1.6–3.9) *vs* 0.71 (0.31–1.4); $P<0.0001$]. There was no significant difference between the treatment groups in blood loss for either tonsillectomy or adenotonsillectomy (Fig. 1), nor was there any difference in the incidence of primary (bleeding requiring intervention within 24 h) or secondary (bleeding requiring readmission) haemorrhage (Table 2). Two of the children required a second operation to achieve adequate haemostasis (one each in the placebo and ibuprofen groups). Both rofecoxib and ibuprofen were well tolerated by the children, with no refusal of medication and no episodes of bronchospasm, pruritis or dizziness. One child in the ibuprofen group developed a mild erythematous, non-itchy rash after surgery, which resolved within 4 h without treatment.

Discussion

Ibuprofen in combination with paracetamol as premedication reduced the need for early supplementary analgesia by almost 50% after tonsillectomy. The clinical importance of this finding is indicated by the higher pain scores at the time of supplementary analgesia in the children requiring early rescue. This equates to fewer distressed children on the ward

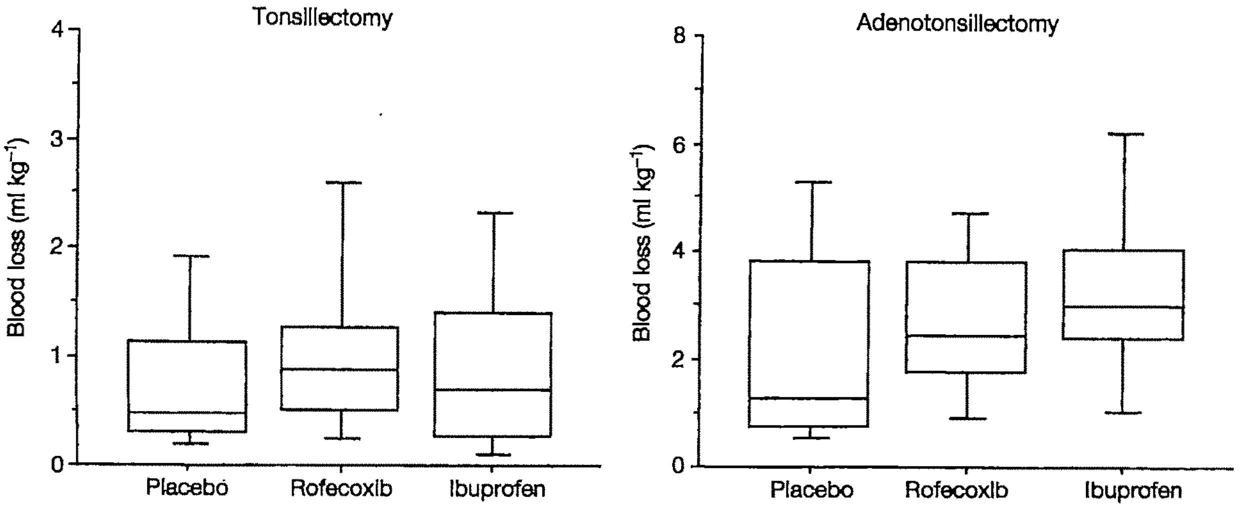

Fig 1 Surgical blood loss Box plots (showing 10th, 25th, 50th, 75th and 90th centiles) of intraoperative blood loss for children having tonsillectomies and adenotonsillectomies according to treatment group There were no significant differences between the groups.

in the early postoperative period in the ibuprofen group. This analgesic benefit from the combination of paracetamol and ibuprofen lends support to our current practice of using NSAIDs for perioperative analgesia.

Paracetamol 20 mg kg^{-1} alone provided adequate analgesia for just 24% of the children in this study. This emphasizes the difficulty in providing pain relief in children with contraindications to NSAIDs. A previous study of paediatric tonsillectomy has shown paracetamol (20 mg kg^{-1}) to be equivalent to diclofenac (1 mg kg^{-1}), but each drug alone was noted to provide inadequate overall analgesia.[11] These results provide some justification for the use of NSAIDs in children with relative contraindications, such as controlled asthmatics, particularly in view of the recent demonstration of the safety of diclofenac in asthmatic children.[22] However, it should be noted that, although the dose of paracetamol (20 mg kg^{-1}) used in this study was our usual oral loading dose, recent studies have demonstrated improved analgesic efficacy with higher doses of oral (40 mg kg^{-1}) or rectal paracetamol (40–60 mg kg^{-1}), which achieve higher plasma concentrations.[9 10] It is possible that the use of a larger loading dose of paracetamol in our study would have produced an improved analgesic effect. Also of relevance to our study is the observation that the premedication of children having adenotonsillectomies with oral paracetamol elixir (40 mg kg^{-1}) has been shown to have no effect on the volume or pH of gastric contents at the time of operation.[23]

The addition of rofecoxib to paracetamol failed to confer any additional analgesic benefit compared with paracetamol alone. This was a surprising finding, which questions the role of COX-2 antagonists for perioperative analgesia. Previous perioperative studies in adults have demonstrated rofecoxib to have an analgesic efficacy equivalent to that of ibuprofen[17 18] and it has been shown to be opioid-sparing after spinal surgery.[24] When designing our study, in the absence of paediatric pharmacokinetic data, we calculated the dose of rofecoxib (0.625 mg kg^{-1}) such that a 40-kg child would receive the current UK maximum adult dose of 25 mg. Our rofecoxib dose calculation was based on the finding that, in adults, a dose of rofecoxib 50 mg is equianalgesic to 400 mg ibuprofen.[17] As the usual paediatric dose of ibuprofen is 5 mg kg^{-1}, we expected a dose of rofecoxib 0.625 mg kg^{-1} to be equianalgesic. This dose also allowed us to give equal volumes of the ibuprofen and rofecoxib drug syrups (0.25 ml kg^{-1}), which assisted with study blinding.

The study drugs were given more than 60 min before surgery, allowing approximately 100 min for rofecoxib absorption and the onset of analgesic action before arrival in the recovery unit. Data from dental extraction studies have indicated that the time to onset of analgesia for rofecoxib is similar to that of ibuprofen[18] and has been quoted by the manufacturer as 45 min. We have no evidence of a delayed analgesic effect of rofecoxib as the total analgesic consumption in the first 24 h was similar across the groups. In seeking to explain our failure to demonstrate any benefit, it is unlikely that our study was under-powered, as we have been able to show the beneficial analgesic effect of ibuprofen.

This study looked for an additive analgesic effect of the combination of rofecoxib and paracetamol. The sites of action of both drugs may be relevant: paracetamol inhibits brain cyclo-oxygenase[25] and rofecoxib inhibits COX-2, which is expressed constitutively in the brain as well as being inducible in the periphery.[16] If both drugs were acting to inhibit the same brain cyclo-oxygenase, we could perhaps explain the lack of additive effect (if we assume that paracetamol is producing nearly maximal antagonism of brain COX). Alternatively, it is possible that inducible

COX-2 does not play a major role in nociception in the early recovery period after tonsillectomy. Our findings suggest that central cyclo-oxygenase and peripheral COX-1 are involved in mediating early pain after tonsillectomy.

The surgical blood loss seen during this study was similar to that reported previously from our institution.[13] There were no significant differences in blood loss or in bleeding complications between the three groups. In designing the study, we wished to reflect our normal clinical practice so no restriction was placed upon surgical grade or technique employed for tonsillectomy. A retrospective power analysis showed that the study had limited power (23%) to demonstrate the largest difference seen between the groups because of the large variation in blood loss. That the observed distributions were so wide suggests that there are factors other than the perioperative use of NSAIDs that determine surgical bleeding.

The incidence of postoperative vomiting was 29% in the first 24 h. This was without prophylactic antiemetic and is lower than that previously reported in this surgical population.[26] Previous studies of tonsillectomy have correlated postoperative vomiting with opioid use[3] and pain.[11] In our study, there were no significant differences between the groups in vomiting or in the need for rescue antiemetic.

In conclusion, this clinical study emphasizes that paediatric tonsillectomy is a painful procedure requiring proactive analgesic strategies to provide a good quality of postoperative recovery. We have shown analgesic benefit without increased risk of complications by combining ibuprofen with paracetamol for premedication. We failed to show an analgesic effect of rofecoxib in combination with paracetamol, suggesting that the COX-2 antagonists will require careful evaluation before their role in perioperative analgesia can be defined clearly. In particular, studies that compare COX-2 antagonists with paracetamol (which, coincidentally, also has a low incidence of gastric and haemostatic complications) will be particularly valuable. There is further scope for improving analgesia after tonsillectomy but we can commend the perioperative combination of ibuprofen with paracetamol as a useful strategy in children.

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BJA

LABORATORY INVESTIGATIONS

Effects of intracoronary calcium chloride on regional oxygen balance and mechanical function in normal and stunned myocardium in dogs

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Background. Brief myocardial ischaemia has been demonstrated to result in mechanical and coronary endothelial dysfunction, in which calcium may play a role. We examined whether the mechanical and vascular responses to calcium are altered in postischaemic, reperfused myocardium.

Methods. Regional myocardial oxygen consumption (MV_{O_2}), mechanical function and coronary blood flow (CBF) in response to calcium chloride (0.10, 0.25, 0.50 and 0.75 mg ml^{-1} of CBF) directly infused into the left anterior descending (LAD) artery were determined before (normal) and 30 min after a 15-min-period of LAD occlusion (stunned) in an open-chest canine model. Percentage segment shortening (%SS) and percentage postsystolic shortening (%PSS) in the LAD territory were determined using ultrasonic crystals and CBF using a Doppler transducer. Myocardial extraction of oxygen (E_{O_2}) and lactate (E_{lac}) was calculated.

Results. The infusion of calcium chloride resulted in dose-dependent increases in %SS and MV_{O_2} but did not affect %PSS in normal myocardium. These changes were accompanied by parallel increases in CBF, resulting in no change in E_{O_2}. In stunned myocardium, the responses to calcium chloride were not significantly altered, with the exception of a reduction in %PSS. However, ischaemia and reperfusion itself significantly reduced %SS and E_{lac} and increased %PSS.

Conclusions. These data suggest that calcium chloride improves regional systolic and diastolic function both in normal and stunned myocardium. Calcium chloride is unlikely to cause direct coronary vasoconstriction or to deteriorate regional mechanical function in postischaemic myocardium.

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A brief ischaemic episode followed by reperfusion results in 'stunned' myocardium, in which the myocardial contractile function is impaired for a prolonged period in the absence of cell necrosis.[1] Myocardial stunning *per se* usually requires no therapy at all, as blood flow is normal and contractile function recovers spontaneously. However, if it is severe or involves parts of the left ventricle large enough to cause impairment of global ventricular function, it can be reversed with inotropic agents.[2–5]

Clinically, calcium is frequently used as an initial therapeutic agent to reverse acute postischaemic ventricular dysfunction during separation from cardiopulmonary bypass.[6] However, calcium has been observed to reduce coronary blood flow (CBF) in an isolated beating heart.[7] A

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recent *in vivo* study also demonstrated that intracoronary calcium chloride caused direct coronary vasoconstriction, in addition to its inotropic action, in normal canine heart.[8]

On the other hand, the stunned myocardium is associated with decreased coronary flow reserve and vasodilator responsiveness.[9 10] Furthermore, it shows normal oxygen consumption ($M\dot{V}_{O_2}$), despite depressed contractile function, i.e. increased oxygen cost of contractility.[11] It is speculated that calcium may exaggerate the vasoconstrictor response and hence impair myocardial oxygen balance in the stunned myocardium. Indeed, it has been demonstrated that mechanical function is not as tightly coupled as CBF and $M\dot{V}_{O_2}$, and thus oxygen extraction (E_{O_2}) increased during inotropic stimulation with dobutamine in postischaemic canine myocardium.[5]

In addition, intracellular Ca^{2+} overloading during ischaemia and reperfusion has been implicated in the pathogenesis of myocardial stunning.[12] In an isolated rat heart, postischaemic myocardium was susceptible to Ca^{2+} influx and subsequent injury.[13] Administration of calcium may therefore deteriorate rather than improve regional function, by augmenting calcium overload in postischaemic myocardium. The seeming paradox of the clinical use and known pathophysiological effects of calcium remains to be explained. In the present work we studied the effects of calcium chloride on regional oxygen balance and mechanical function in the stunned myocardium.

Methods

The study was approved by the Institutional Review Board of Experimental Animal Research. Mongrel dogs of either sex, weighing 17–35 kg, were anaesthetized with thiopental sodium (10–15 mg kg^{-1} i.v.). After tracheal intubation, anaesthesia was maintained with enflurane (1.4% end-tidal; Datex, Helsinki, Finland) in 100% oxygen by positive-pressure ventilation. In eight dogs, anaesthesia was induced with an i.v. bolus injection of fentanyl 100 μg kg^{-1} and midazolam 0.6 mg kg^{-1} and maintained by continuous infusion at rates of 20.0 μg kg^{-1} h^{-1} and 0.6 mg kg^{-1} h^{-1} respectively. Tidal volume and respiratory rate were adjusted to maintain end-tidal carbon dioxide concentration between 4.5 and 5.5%. To obtain muscle relaxation, vecuronium bromide 0.1 mg kg^{-1} was used initially as a bolus and thereafter infused at 0.05 mg kg^{-1} h^{-1}. Body temperature and electrocardiogram were monitored continuously. Ringer's lactate solution was administered i.v. at 5 ml kg^{-1} h^{-1}.

A left thoracotomy was performed via the fifth intercostal space and the heart was suspended in a pericardial cradle. Instruments were implanted in and around the heart as shown in Fig. 1. A Doppler transit time flow probe (Transonic Systems, Ithaca, NY, USA) was placed around the main pulmonary artery to measure cardiac output, and another flow probe was placed around the left anterior descending coronary artery (LAD) distal to the first diagonal branch for continuous blood flow measurement. A rubber band was placed around the LAD immediately distal to the flow probe to serve as an occluder. For the infusion of drugs, a 24-gauge catheter was inserted into the proximal LAD. A pair of ultrasonic dimension transducers (Medical Research Technology, Gaithersburg, MD, USA) were implanted approximately 10 mm apart in the subendocardium of a region of anterior wall that demonstrated myocardial cyanosis during a brief test occlusion of the LAD. A catheter-tipped micromanometer (SPR-524; Millar Instruments, Houston, TX, USA) was inserted directly into the left ventricle via an apical incision for the measurement of left ventricular pressure (LVP). The first derivative of LVP ($+dP/dt_{max}$ and $-dP/dt_{min}$) was obtained by electronic differentiation. The right femoral artery was cannulated for measurement of aortic pressure with a catheter-tipped micromanometer and for blood sampling to measure arterial oxygen and lactate contents. An 18-gauge catheter was inserted into the left atrium for the measurement of luminal pressure (Datex, Helsinki, Finland) and a 24-gauge catheter into the anterior interventricular vein at the same level as the LAD occluder for measurement of coronary venous oxygen and lactate concentrations [14]

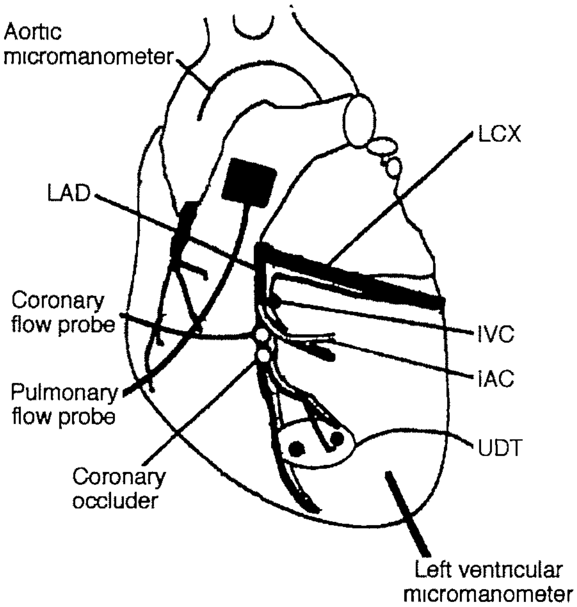

Fig 1 Schematic presentation of the experimental preparation LAD=left anterior descending coronary artery, LCX=left circumflex coronary artery, IVC=intravenous catheter, IAC=intra-arterial catheter, UDT=ultrasonic dimension transducers.

Oxygen (Gem Premier; Instrumentation Laboratory, Lexington, MS, USA) and lactate concentrations (Vitros 950; Ortho-Clinical Diagnostics, Rochester, NY, USA) were measured in blood drawn simultaneously from the coronary vein and artery. $M\dot{V}_{O_2}$ of the anterior myocardial wall was calculated by multiplying the arteriovenous oxygen difference by total LAD flow. E_{O_2} and myocardial lactate extraction (E_{lac}) (as a percentage) were calculated by dividing the arteriovenous difference by the arterial content. Plasma Ca^{2+} concentrations were also measured from the anterior interventricular venous blood with a blood gas analyser (Gem Premier; Instrumentation Laboratory, Lexington, MS, USA).

After a stabilization period of 60 min, pre-infusion mechanical and haemodynamic data were collected in one group of 16 dogs (series 1). Simultaneous measurements were obtained of arterial and coronary venous oxygen and lactate concentrations (metabolic data). The animals then received intracoronary infusions of calcium chloride with a syringe pump (STC 524; Terumo, Japan). Calcium chloride was infused in incremental concentrations of 0.10, 0.25, 0.50 and 0.75 mg ml^{-1} LAD flow for 3–5 min, each administered 8–10 min apart. The infusion rate was calculated by multiplying the desired concentration by LAD blood flow, resulting in a rate between 0.3 and 2.0 ml min^{-1}. All measurements except metabolic data at 0.50 mg ml^{-1} were repeated at the end of each dose and 5 min after calcium chloride infusion was stopped. Because mechanical and CBF responses to calcium chloride at 0.50 mg ml^{-1} did not differ significantly from those at 0.75 mg ml^{-1} and myocardial oxygen balance was well maintained, metabolic data at 0.50 mg ml^{-1} were not obtained. After one series of experiments in normal myocardium, all dogs were subjected to a 15-min LAD occlusion and subsequent reperfusion to stun the myocardium. Approximately 30 min after the onset of reperfusion, when haemodynamic and flow values were stable, the same calcium chloride infusion protocol was repeated.

In eight dogs (series 2), experiments were performed to evaluate whether preischaemic administration of calcium chloride altered postischaemic contractile responsiveness (preconditioning against postischaemic contractile dysfunction) and whether volatile anaesthetics affected postischaemic myocardial responsiveness. To address the first issue, calcium chloride was infused only in the postischaemic myocardium. To address the second issue, fentanyl—midazolam instead of enflurane was used to maintain anaesthesia. The responses to intracoronary infusions of calcium chloride (0.10, 0.25, 0.50 and 0.75 mg ml^{-1} of LAD flow) were assessed using a protocol similar to that used for series 1.

Data acquisition and analysis

Blood flow (main pulmonary artery and LAD), the segmental dimension of the anterior wall and pressures (LVP and mean aortic pressure) were monitored continuously and recorded on a polygraph (TA 5000; Gould, Cleveland, OH, USA). End-systolic segment length (ESL) was determined approximately 20 ms before peak $-dP/dt_{min}$ and end-diastolic segment length (EDL) was determined at the onset of left ventricular isovolumetric contraction.[15] Steady beat data were obtained from three to five cardiac cycles. Regional myocardial contractility was determined using percentage segment shortening (%SS), calculated from the equation $\%SS=[(EDL-ESL)/EDL]\times 100$. Percentage postsystolic shortening (%PSS), as a regional diastolic function, was calculated from the equation $\%PSS=[(ESL-L_{min}D)/(L_{max}-L_{min}D)]\times 100$, where $L_{min}D$ and L_{max} are minimum length during diastole and maximum length in an overall contraction, respectively. Coronary perfusion pressure was calculated as aortic diastolic pressure minus left atrial pressure.

At the end of the experiment, the heart was stopped by intra-atrial injection of concentrated potassium chloride solution. The area supplied by the LAD artery was defined by injection of Evans blue into the vessel at the site of the flow transducer. Weighing of the stained muscle allowed calculation of mean flow in ml min^{-1} per 100 g of muscle. The LAD perfusion territory was 24.3 (5.6)% of the total left ventricular mass.

Statistical analysis

All data are presented as mean (SD). They were analysed using StatView software version 4.0 (Abacus Concepts, Berkeley, CA, USA) on a Macintosh computer. Statistical analysis of the calcium chloride responses in normal and stunned myocardium was performed by two-way analysis of variance for repeated measures followed by Dunnett's *t* test. Comparisons between the pre-infusion values of normal and stunned myocardium were made with the paired Student's *t*-test. Enflurane- and fentanyl–midazolam-anaesthetized groups were compared using the Mann–Whitney *U*-test. Linear regression analysis was used to examine the relationship between CBF and $M\dot{V}_{O_2}$ at all doses of calcium chloride in series 1. Significance was assumed when $P<0.05$.

Results

Two of 18 dogs anaesthetized with enflurane produced lactate before the experiment and three died of ventricular fibrillation immediately after the onset of reperfusion, whereas three of eight dogs anaesthetized with fentanyl—midazolam developed ventricular fibrillation during coronary occlusion or immediately after the onset of reperfusion. These were excluded from data analysis.

Table 1 shows systemic haemodynamics in normal and stunned myocardium in enflurane-anaesthetized dogs. Calcium chloride was without significant effects on these variables in normal myocardium. However, there was a dose-dependent increase in $+dP/dt_{max}$. LAD occlusion produced a small increase in heart rate and left atrial pressure and decreased mean aortic pressure, $+dP/dt_{max}$, $-dP/dt_{min}$ and cardiac index. They quickly returned towards baseline values at the onset of reperfusion, with the exception of $+dP/dt_{max}$ and $-dP/dt_{min}$, which remained lower than their baseline values. In stunned myocardium,

Table 1 Effects of increasing infusion rate of intracoronary calcium chloride on systemic haemodynamics before (normal) and 30 min after a 15-min coronary occlusion (stunned) in enflurane-anaesthetized dogs. HR = heart rate, MAP = mean aortic pressure; $+dP/dt_{max}$ = maximum positive left ventricular pressure derivative; $-dP/dt_{min}$ = minimum negative left ventricular pressure derivative; LAP = left atrial pressure, CI = cardiac index, CPP = coronary perfusion pressure; CBF = coronary blood flow Results are mean (SD) of data from 13 dogs $^*P<0.05$ compared with pre-infusion values; $^†P<0.05$ compared with normal myocardium

Variable	Condition	Pre-infusion	Calcium chloride (mg ml^{-1} CBF)			
			0.10	0.25	0.50	0.75
HR (beats min^{-1})	Normal	132 (16)	131 (18)	131 (17)	130 (16)	131 (21)
	Stunned	133 (18)	133 (19)	134 (18)	136 (23)	139 (23)
MAP (mm Hg)	Normal	87 (12)	87 (12)	89 (13)	89 (14)	92 (15)
	Stunned	84 (10)	84 (10)	84 (10)	84 (9)	84 (8)
$+dP/dt_{max}$ (mm Hg s^{-1})	Normal	1685 (497)	1749 (489)	1873 (547)*	1896 (617)*	1987 (646)*
	Stunned	1316 (190)†	1403 (203)	1488 (266)*	1664 (209)*	1787 (251)*
$-dP/dt_{min}$ (mm Hg s^{-1})	Normal	2480 (501)	2526 (504)	1495 (438)	2478 (493)	2421 (544)
	Stunned	2149 (372)†	2165 (438)	2090 (429)	2050 (513)	2182 (426)
LAP (mmHg)	Normal	5.2 (1.0)	5.1 (1.0)	5.3 (1.0)	5.3 (1.1)	5.3 (1.2)
	Stunned	5.9 (0.9)	5.8 (0.9)	5.4 (0.9)	5.3 (1.1)	5.2 (0.9)
CI (litre min^{-1}m^{-2})	Normal	2.3 (0.5)	2.3 (0.5)	2.2 (0.5)	2.2 (0.6)	2.1 (0.5)
	Stunned	2.1 (0.7)	2.1 (0.7)	2.1 (0.7)	2.1 (0.5)	2.1 (0.6)
CPP (mmHg)	Normal	73 (11)	74 (8)	75 (7)	76 (8)	76 (9)
	Stunned	71 (10)	71 (11)	72 (8)	72 (10)	72 (11)

Table 2 Effects of increasing infusion rate of intracoronary calcium chloride on regional mechanical function before (normal) and 30 min after a 15-min coronary occlusion (stunned) in enflurane-anaesthetized dogs. %SS = percentage systolic shortening; EDL = end-diastolic segment length, ESL = end-systolic segment length, %PSS = percentage postsystolic shortening All length measures are normalized to an initial end-diastolic length of 10 mm at baseline Results are mean (SD) of data from 13 dogs $^*P<0.05$ compared with pre-infusion values, $^†P<0.05$ compared with normal myocardium

Variable	Condition	Pre-infusion	Calcium chloride (mg ml^{-1} CBF)			
			0.10	0.25	0.50	0.75
%SS	Normal	16.9 (4.3)	18.1 (4.5)*	20.2 (4.8)*	22.4 (5.1)*	23.6 (5.6)*
	Stunned	7.4 (4.5)†	9.9 (4.7)*	14.3 (5.9)*	18.8 (4.9)*	21.5 (6.7)*
EDL (mm)	Normal	10.0 (0.00)	9.95 (0.10)	9.88 (0.23)*	9.84 (0.13)*	9.83 (0.19)*
	Stunned	10.5 (0.37)†	10.27 (0.36)	10.20 (0.33)*	10.03 (0.25)*	9.88 (0.35)*
ESL (mm)	Normal	8.4 (0.43)	8.24 (0.43)	7.99 (0.51)*	7.79 (0.52)*	7.65 (0.51)*
	Stunned	9.68 (0.78)†	9.37 (0.85)	9.04 (0.89)*	8.34 (0.54)*	8.04 (0.59)*
%PSS	Normal	5.9 (2.9)	5.5 (3.6)	4.2 (4.5)	3.5 (6.4)	3.7 (5.6)
	Stunned	32.7 (17.6)†	20.1 (17.6)*	14.7 (19.8)*	5.5 (4.7)*	5.8 (5.3)*

the effects of calcium chloride were similar to those in normal myocardium.

Table 2 shows the effects of calcium chloride on regional mechanical function in normal and stunned myocardium in enflurane-anaesthetized dogs. Calcium chloride caused dose-dependent increases in %SS and decreases in ESL but did not affect %PSS in normal myocardium. LAD occlusion rapidly increased EDL [from 10.0 to 10.8 (0.38), $P<0.01$] and %PSS [from 5.9 (2.9) to 76 (10)%, $P<0.01$], systolic bulging apparent within 1–3 min. Subsequent reperfusion produced a transient increase in %SS followed by a gradual decline to 7.4 (4.5)% (44% of preischaemic baseline) at 30 min of reperfusion. In stunned myocardium, the responses to calcium chloride were not altered compared with those in normal myocardium, except for a progressive reduction in %PSS. When calcium chloride was stopped, %SS rapidly returned towards, but not below, pre-infusion values in stunned myocardium (data not shown).

Table 3 shows the effects of calcium chloride on CBF and metabolic data in normal and stunned myocardium in enflurane-anaesthetized dogs. Calcium chloride caused dose-dependent increases in $M\dot{V}_{O_2}$ and CBF in normal myocardium. After LAD occlusion and reperfusion, metabolic and CBF responses to calcium chloride were not altered significantly, while there was a slight decrease in $M\dot{V}_{O_2}$ from preischaemic baseline values of normal myocardium ($P<0.05$), despite severely impaired contractile function. During calcium chloride infusion, CBF increased linearly in relation to $M\dot{V}_{O_2}$ in normal and stunned myocardium (Fig. 2), such that that E_{O_2} remained unchanged. Plasma Ca^{2+} concentrations in the anterior interventricular vein were dose-dependently increased by the administration of calcium chloride to a similar extent in normal and stunned myocardium, implying that coronary veins draining the LAD region were correctly cannulated.

Figure 3 shows the effects of calcium chloride on lactate extraction in enflurane-anaesthetized dogs. Although significantly reduced by the ischaemia and reperfusion insult itself, E_{lac} was not affected by calcium chloride either in normal or stunned myocardium. However, four of 13

Table 3 Effects of increasing infusion rate of intracoronary calcium chloride on coronary blood flow (CBF) and metabolism before (normal) and 30 min after a 15-min coronary occlusion (stunned) in enflurane anaesthetized dogs $M\dot{V}_{O_2}$ = myocardial oxygen consumption; E_{O_2} = myocardial oxygen extraction Results are mean (SD) of data from 13 dogs *$P<0.05$ compared with pre-infusion values; †$P<0.05$ compared with normal myocardium

Variable	Condition	Pre-infusion	Calcium chloride (mg ml^{-1} CBF)			
			0.10	0.25	0.50	0.75
CBF (ml min^{-1} 100 g^{-1})	Normal	73.1 (7.0)	78.9 (8.9)*	86.6 (9.4)*	95.2 (10.1)*	101.5 (9.9)*
	Stunned	70.9 (6.4)	78.0 (6.7)*	86.4 (6.0)*	93.0 (10.3)*	99.5 (11.6)*
Arterial P_{O_2} (mm Hg)	Normal	380 (67)	378 (65)	383 (65)	–	383 (65)
	Stunned	389 (85)	387 (84)	388 (85)	–	389 (85)
Coronary venous P_{O_2} (mm Hg)	Normal	30.4 (3.5)	30.7 (3.3)	30.5 (2.9)	–	30.8 (3.4)
	Stunned	32.2 (4.9)	32.5 (5.0)	32.2 (5.0)	–	31.7 (3.8)
$M\dot{V}_{O_2}$ (ml min^{-1} 100 g^{-1})	Normal	7.1 (1.5)	7.6 (1.6)*	8.4 (1.8)*	–	9.9 (2.1)*
	Stunned	6.3 (1.3)†	6.9 (1.3)*	8.0 (1.8)*	–	9.0 (2.1)*
E_{O_2} (%)	Normal	52.1 (8.2)	52.5 (7.3)	52.5 (6.9)	–	52.5 (6.9)
	Stunned	49.4 (9.0)†	49.8 (8.6)	50.5 (9.1)	–	50.7 (9.1)
Ca^{2+} in coronary vein (mmol litre^{-1})	Normal	1.08 (0.13)	1.68 (0.43)*	2.96 (0.59)*	–	5.03 (0.97)*
	Stunned	1.14 (0.11)	1.70 (0.47)*	2.88 (0.49)*	–	5.29 (0.72)*

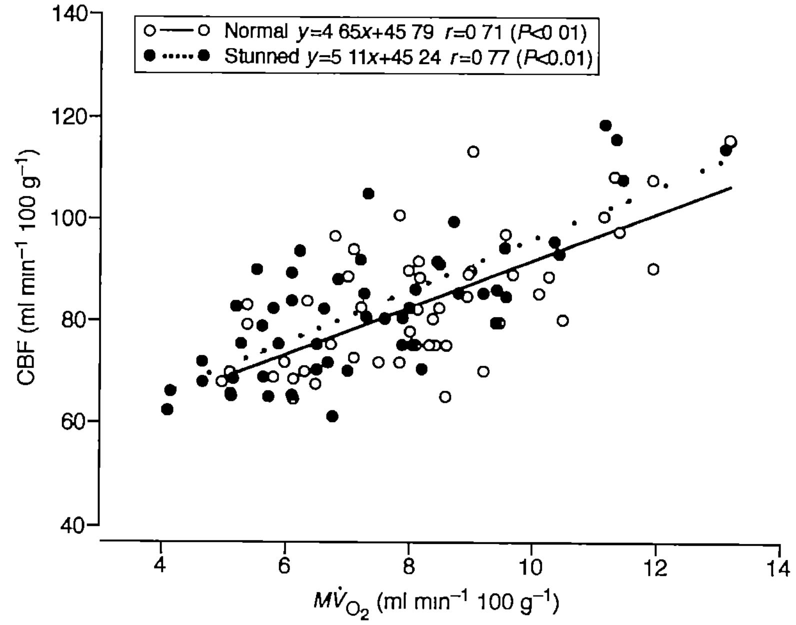

Fig 2 Relationship between myocardial oxygen consumption ($M\dot{V}_{O_2}$) and coronary blood flow (CBF) during intracoronary calcium chloride infusion in normal and stunned myocardium in enflurane anaesthetized dogs (n=13) In both normal and stunned myocardium, CBF increased in parallel with $M\dot{V}_{O_2}$.

animals anaesthetized with enflurane showed lactate production with the highest dose of calcium chloride in stunned myocardium.

Figure 4 compares the effects of calcium chloride on %SS, $M\dot{V}_{O_2}$, CBF and E_{O_2} in stunned myocardium in enflurane- and fentanyl–midazolam-anaesthetized dogs. Calcium chloride produced similar increases in %SS and $M\dot{V}_{O_2}$. The increase in CBF was proportional to $M\dot{V}_{O_2}$, and therefore E_{O_2} remained unchanged in both groups. In addition, systemic haemodynamic variables, including cardiac index, +dP/dt_{max} and heart rate, did not differ significantly between enflurane- and fentanyl–midazolam-anaesthetized dogs (data not shown).

Discussion

The present study demonstrated that calcium chloride improved regional contractile and diastolic function in stunned canine myocardium. In addition, %SS returned to the postischaemic baseline value after discontinuation of inotropic stimulation with calcium chloride. Indeed, restoration of normal contractile capability during infusion of calcium has been observed in isolated globally ischaemic rat hearts[16] and *in vivo* regionally ischaemic hearts in dogs[3 12] and pigs.[4 17] These findings are contradictory to the previous notion that Ca^{2+} overloading occurring during ischaemia and reperfusion is causally related to the pathogenesis of

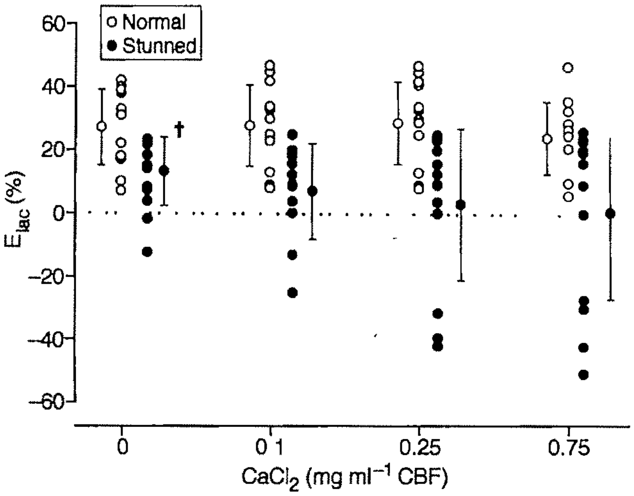

Fig 3 Effects of calcium chloride on lactate extraction (E_{lac}) in normal and stunned myocardium in enflurane-anaesthetized dogs (n=13). E_{lac} was not significantly affected by calcium chloride either in normal or stunned myocardium Data are skewed and therefore presented as a dot plot with mean (SD). The ischaemia- and reperfusion insult itself significantly reduced E_{lac}. †P<0.05 compared with normal myocardium.

myocardial stunning.[12] Moreover, calcium chloride administered early during reperfusion has been shown to elicit a dose-dependent deterioration in ventricular function in the isolated postischaemic rat heart.[13] Viable cells may restore control of cytoplasmic Ca^{2+} rapidly after ischaemia, and hence intracellular Ca^{2+} levels return to a baseline value after 20 min of reperfusion.[18] Collectively, the data suggest that calcium chloride may improve rather than deteriorate regional function if administered after, but not during, the early reperfusion period.

Vascular dysfunction may occur even after a short period of ischaemia.[9 10] The vascular response to endothelium-dependent dilators (e.g. acetylcholine) was reduced, whereas that to constrictors (e.g. the thromboxane mimic U46619) was enhanced after 15 min of regional ischaemia in canine hearts *in situ*.[10] Therefore, the vascular response to calcium chloride may differ between normal and stunned myocardium. However, the response to calcium chloride, increased CBF with no significant changes in coronary venous oxygen tension and E_{O_2}, did not differ significantly between normal and stunned myocardium (Table 3). Similarly, Buffington and Rothfield[4] observed an appropriate increase in CBF when regional contractility was stimulated by calcium chloride in stunned porcine myocardium. These findings suggest that, in stunned myocardium, calcium chloride does not interfere with normal metabolic vasoregulation but maintains CBF in proportion to the myocardial oxygen demand.

In contrast, Crystal and colleagues[8] demonstrated that intracoronary calcium chloride produced direct vasoconstriction and impaired coupling of CBF to the augmented myocardial oxygen demand in normal myocardium of dogs anaesthetized with fentanyl–midazolam. The discrepancy between these studies is not readily explained. It has been shown that volatile anaesthetics decrease Ca^{2+} sensitivity in rat aortic vascular smooth muscle *in vitro*[19] and produce coronary vasodilation directly in *in situ* canine hearts.[20] However, the vascular responses to calcium chloride were similar in fentanyl–midazolam- and enflurane anaesthetized dogs in the present study (Fig. 4). It is unlikely that anaesthetics are responsible for the discrepancy between these studies. Another possible explanation may include different experimental methods. Crystal and colleagues[8] used an extracorporeal perfusion system with a pressurized reservoir to keep coronary perfusion pressure constant, whereas we administered calcium chloride directly into the LAD. However, the coronary perfusion pressure was not affected by calcium chloride in either study.

The markedly reduced contractile function has been associated with an unaltered $M\dot{V}_{O_2}$ in stunned myocardium.[11] If contractile function increases at a higher energy cost in stunned myocardium, an elevated CBF would be expected for a given level of function (assuming unchanged E_{O_2}). However, the CBF response in relation to segment shortening was similar in normal and stunned myocardium in the present study. Chiu and colleagues[21] have demonstrated that regional inotropic stimulation with isoproterenol restores synchrony and regional work in stunned myocardium without greatly affecting $M\dot{V}_{O_2}$ in dogs. They speculated that myocardial stunning produced asynchrony between force development and segment shortening, thereby decreasing systolic regional work (but not total work) to a greater extent than $M\dot{V}_{O_2}$. It is likely that inotropic drugs, including calcium chloride, do not increase total mechanical work but restore the synchrony, resulting in no greater increases in CBF relative to regional mechanical work in stunned myocardium.

Although systolic function associated with the use of inotropic drugs has been studied extensively in stunned myocardium, the diastolic function has been overlooked. In the present study, calcium chloride did not affect peak −dP/dt_{min} but produced a progressive reduction in %PSS (Table 2). Similarly, Schlack and colleagues[22] observed that intracoronary norepinephrine did not affect peak −dP/dt_{min} but reduced postejection wall thickening in an open-chest canine model. It is also likely that calcium chloride improves early diastolic function. On the other hand, peak −dP/dt_{min} has been demonstrated to reflect changes in contractility (i.e. peak ventricular pressure) rather than relaxation in regionally ischaemic canine hearts.[23] The unaltered aortic pressure during the infusion of calcium chloride in the present study may be related to the unaltered peak −dP/dt_{min}. There has been debate about whether calcium chloride increases chamber stiffness (late diastolic dysfunction) in postischaemic myocardium. Gao and colleagues[24] observed that, in response to supraphysiological increases in [Ca^{2+}]$_o$, diastolic [Ca^{2+}]$_i$ and tone increased in stunned trabeculae, with frequent occurrence of after-contractions in the isolated rat heart. They speculated that

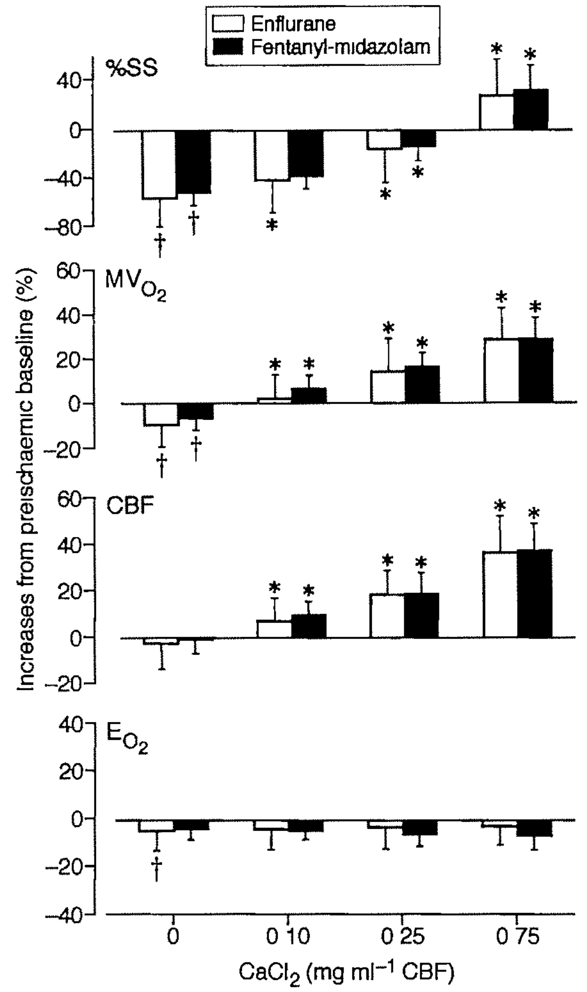

Fig 4 Changes [mean (SD)] from preischaemic baseline values of %SS, $M\dot{V}_{O_2}$, CBF and E_{O_2} during calcium chloride infusion in stunned myocardium in dogs anaesthetized with enflurane (n=13) or fentanyl–midazolam (n=5) Changes were similar in the two groups. †P<0.05 compared with preischaemic baseline values; *P<0.05 compared with postischaemic baseline values (indicated as dose 0 of calcium chloride)

increased susceptibility to Ca^{2+} results in increased diastolic tone under conditions that favour cellular Ca^{2+} accumulation. DeHert and colleagues[25] also found an increase in ventricular stiffness when calcium chloride was given early after cardiopulmonary bypass, suggesting temporary diastolic dysfunction. In contrast, Eberli and colleagues[26] observed that increased $[Ca^{2+}]_i$ was not causally related to the increase in diastolic chamber stiffness in isolated rat hearts.

The effect of calcium chloride on myocardial function is transient, despite persistent elevation of the plasma concentration of ionized calcium, whereas the effect on systemic vascular resistance is more prolonged.[27] We therefore chose to infuse calcium chloride continuously rather than use a single bolus injection to produce steady-state changes in myocardial contractility (and hence myocardial oxygen demand), as shown previously by Crystal and colleagues.[8] In general, calcium chloride at doses of 5–15 mg kg^{-1} body weight is given i.v. to improve haemodynamics while the patient is weaned from cardiopulmonary bypass.[28] An i.v. bolus administration of calcium chloride at a dose of 15 mg kg^{-1} caused a maximal increase of approximately 0.8 mmol litre^{-1}.[29] Therefore, our data with the lowest rate of calcium chloride (0.1 mg ml^{-1}=0.9 mmol litre^{-1}) appears to be clinically relevant.

Lactate production has been a reliable sign of a mismatch between myocardial oxygen demand and supply.[30] In the present study, a progressive reduction in lactate extraction was observed during the infusion of calcium chloride in stunned myocardium, albeit statistically insignificant. Moreover, lactate was produced in four of 13 animals anaesthetized with enflurane during calcium chloride infusion at 0.75 mg ml^{-1} in stunned myocardium (Fig. 3). Stahl and colleagues[31] observed increased heterogeneity of oxygen extraction with very low venous oxygen saturation in stunned myocardium despite patent microvasculature and normal perfusion, implying either focally impaired perfusion or increased metabolic activity. Calcium chloride would have induced focal microcirculatory changes with localized areas of tissue hypoxia and anaerobic metabolism, leading to lactate production, despite unaltered coronary venous oxygen tension. In addition, increased susceptibility to Ca^{2+} load in stunned myocardium has been demonstrated in isolated rat hearts.[13 24] Indeed, functional deterioration has been reported after intense inotropic stimulation with high-dose dobutamine in many reperfused segments that respond positively to low-dose dobutamine infusion, probably because of impaired intracellular Ca^{2+} handling.[32] Likewise, calcium chloride may have a deleterious long-lasting effect that differs from an immediate functional and metabolic effect, as in the present study. Therefore, caution should be exercised in extrapolating our results, showing that the postischaemic dysfunction was effectively improved by calcium chloride without impairing myocardial oxygen balance, to the clinical situation.

The present study has several limitations. First, enflurane was used to maintain anaesthesia. Volatile anaesthetics have been shown to enhance recovery of postischaemic myocardium[33] and to produce coronary vasodilation directly *in vivo*.[20] Enflurane may have protected the myocardium against ischaemia and reperfusion injury, altering the response to calcium chloride. However, we observed that responses to calcium chloride in postischaemic myocardium were similar in enflurane- and fentanyl–midazolam-anaesthetized groups (Fig. 4). Secondly, it has been demonstrated that calcium chloride has a preconditioning effect against postischaemic contractile dysfunction.[34] However, the responses to calcium chloride in the stunned myocardium were similar in series 1 and series 2 (Fig. 4). It is unlikely that a preconditioning effect was exerted in our experimental protocol. Thirdly, the present study did not evaluate the time course of recovery of postischaemic, reperfused myocardium during the period corresponding to drug infusion (30–70 min of reperfusion). However, an open-chest canine model has shown constant regional contractile function (%SS) between 30 and 90 min of reperfusion.[35] Furthermore, %SS returned to the pre-infusion values after cessation of calcium chloride infusion. Finally, changes in heart rate and systemic blood pressure during calcium chloride infusion may result in increases in $M\dot{V}_{O_2}$ and CBF. However, calcium chloride did not affect aortic pressure, heart rate or coronary perfusion pressure at any time during the study.

In summary, calcium chloride improved regional systolic and diastolic functions both in normal and stunned myocardium. However, the metabolic control of CBF is unlikely to be impaired in stunned myocardium, as shown by an enhanced regional function in association with proportional increases in CBF. In addition, calcium chloride is unlikely to deteriorate regional mechanical function in postischaemic myocardium.

Acknowledgement

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Naloxone prevents increased atrial natriuretic peptide release during regional myocardial ischaemia and stunning in awake dogs

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Background. Atrial natriuretic peptide (ANP) release is increased in patients with ischaemic left ventricular dysfunction. A beneficial effect of naloxone on recovery from myocardial stunning was shown previously. The aim of this study was to investigate the effects of naloxone on ANP release during regional myocardial ischaemia and stunning in awake dogs.

Methods. Ten dogs were chronically instrumented for measurement of heart rate, left atrial, aortic, and left ventricular pressure (LVP), LV $dP\cdot dt_{max/min}^{-1}$, and myocardial wall-thickening fraction. An occluder around the left anterior descending artery (LAD) allowed induction of reversible ischaemia in the LAD-perfused myocardium. Each dog underwent two ischaemic episodes (randomized crossover fashion; separate days): 10 min of LAD occlusion (1) after application of naloxone (63 $\mu g\ kg^{-1}$), and (2) without naloxone. ANP levels were measured at baseline (BL) and at predetermined time points until complete recovery of myocardial stunning occurred.

Results. LAD ischaemia-induced release of ANP (peak level: 182 (30) *vs* 27 (7) pg ml^{-1} BL) only in the control group without naloxone. Between 1 and 180 min of reperfusion, ANP levels were significantly higher only in the control group ($P<0.05$).

Conclusion. Pre-ischaemic application of naloxone prevents this ischaemia-induced ANP-release in conscious dogs.

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Keywords: complications, myocardial stunning; antagonists opioid, naloxone; heart, atrial natriuretic peptide; brain, natriuretic peptide; heart, ischaemia

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The natriuretic peptide family consists of a group of structurally similar but genetically distinct peptides. Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), both of myocardial origin, are reactive hormones whose elevated blood levels correlate with myocardial dysfunction, in the presence of cardiac failure. They are similarly upregulated in heart failure and counteract neurohormones that induce vasoconstriction and fluid retention.[1] However, responses of the natriuretic peptides during regional myocardial ischaemia and stunning remain uncertain. Myocardial stunning is a general term for the mechanical dysfunction that persists after reperfusion even in the absence of irreversible damage and despite the return of normal, near-normal, or supranormal perfusion.[2] In a previous investigation, we demonstrated that naloxone attenuates myocardial stunning in conscious dogs through its action on the central nervous system.[3] This effect of naloxone might be explained by antagonizing endogenous opioid peptides (EOPs) which are released upon myocardial ischaemia and have negative inotropic properties.[4]

The present investigation in chronically instrumented conscious dogs tests the hypothesis that (1) ANP and BNP

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are released in response to myocardial regional ischaemia and stunning and (2) that naloxone prevents this ischaemia-induced release.

Methods

This investigation is performed in accordance with the *Guide for the Care and Use of Laboratory Animals*[5] and was approved by the District Government of Münster. After overnight fasting, 10 mongrel dogs (either sex, weight 23–32 kg) received i.m. pre-medication with piritramide 1 mg kg^{-1} and ketamine 5 mg kg^{-1}. The animals were anaesthetized i.v. with propofol 5 mg kg^{-1}. After tracheal intubation, anaesthesia was maintained with isoflurane in a mixture of oxygen (35%) in air and supplemented by fentanyl (5 $\mu g\ kg^{-1}$). Perioperative antibiotic prophylaxis was achieved with cefamandole 30 mg kg^{-1}. Details of the instrumentation methods have been published previously[6] and are summarized briefly belown. A left thoracotomy was performed at the fifth intercostal space under aseptic conditions. Size 18 F gauge catheters were inserted into the descending aorta and the left atrium for pressure measurement, injection of microspheres, administration of naloxone, and withdrawal of blood. A pressure microtransducer (Janssen Pharmaceutica, Beerse, Belgium) was inserted into the left ventricle through an apical stab wound to measure left ventricular pressure (LVP). Pulsed Doppler blood flow velocity probes (20 MHz; Baylor College of Medicine, Houston, TX, USA) were fitted around the left anterior descending coronary artery (LAD). To measure the regional myocardial wall-thickening fraction (WTF), 10 MHz pulsed Doppler crystals were sutured to the myocardium in the LAD-perfused area. Proximal to the Doppler flow probe, a pneumatic occluder was positioned around the LAD (proximal to the first main diagonal branch) to induce reversible brief ischaemic episodes in the LAD-perfused myocardium. After closure of the thorax, all leads were tunnelled subcutaneously and exteriorized between the scapulae. After instrumentation, the animals were trained daily to accustom them to the experimental environment and to ensure that they could quietly lie in the cage when connected to the data acquisition system. Aortic and left atrial pressures were measured using disposable pressure transducers. Pressure, flow velocity, and wall-thickening signals were processed using a six-channel pulsed Doppler system (Baylor College of Medicine). The left ventricular micromanometer was calibrated to the pressures measured in the aorta and left atrium. The LVP signal was electronically differentiated (Gould Inc., Cleveland, OH, USA) to obtain LV $dP{\cdot}dt_{max}^{-1}$ and LV $dP{\cdot}dt_{min}^{-1}$. All signals were digitally recorded. Experiments were only conducted after the animals had recovered completely from the instrumentation, and measurements of blood gas values and haemodynamic variables showed normal values, which took between 10 and 12 days after surgery.

Arterial blood samples for measurement of ANP and BNP were drawn from the aortic catheter, collected into chilled syringes and transferred to polypropylene tubes containing EDTA (1 mg ml^{-1} of blood) and aprotinin (500 kIU ml^{-1} of blood). Thereafter, the samples were centrifuged and the plasma stored at –70°C until analysis. ANP and BNP plasma concentrations were analysed by radioimmunoassays using a polyclonal rabbit IgG-antisera raised to the following peptides (Peninsula Laboratories, Belmont, CA, USA): α-ANP 1–28 (human) and BNP-32 (human). Peptides were extracted from 3 ml plasma (Sep-Pak C_{18}, Waters Associates, Milford, MA, USA) and eluted with 3 ml of a mixture of 60% acetonitrile, 0.1% trifluoroacetic acid, and 39% distilled water (by volume). All samples were assayed in triplicate. Standard curves were constructed with standard human ANP and BNP in radioimmunoassay buffer. The mean recovery of added natriuretic peptides from plasma was 60–80%, and the lower detection limits as defined by 95% of the upper plateau of the standard curve were 0.1 nmol per tube for ANP and 0.5 nmol per tube for BNP. Cross reactivity between natriuretic peptides was less than 0.1%. The intra-assay and inter-assay coefficients of variation were 3.8 and 9.6% for ANP and 6.1 and 7.9% for BNP, respectively.

The experimental design was as follows: All 10 dogs were used in two ischaemic experiments. Each dog had one ischaemic episode without pre-treatment and the other ischaemic episode after pre-treatment with 63 $\mu g\ kg^{-1}$ naloxone (Curamed Pharma, GmbH, Ch.-B.: 0060697) i.v. 5 min before ischaemia.[3] Five animals received their first coronary artery occlusion without pre-treatment. The other five received naloxone before their first ischaemia.

The following observations were made.

1. Measurement of baseline (BL) values in the awake state and induction of 10 min of LAD ischaemia, with follow-up of WTF, ANP, and BNP levels until complete recovery occurred.
2. Measurement of BL values in the awake state, application of 63 $\mu g\ kg^{-1}$ naloxone, induction of 10 min of LAD ischaemia, with follow-up of WTF, ANP, and BNP levels until complete recovery occurred.

A second ischaemic episode was only induced when there was complete recovery of regional myocardial function in the LAD-perfused area; the minimum time interval between the two experiments was 4 days.

Regional myocardial blood flow was measured using coloured microspheres (Triton Technology, San Diego, CA, USA). For each measurement, a total of 9×10^6 microspheres suspended in a volume of 3 ml 0.9% NaCl was injected into the left atrium. The reference blood sample was withdrawn from the aortic catheter at a rate of 10 ml min^{-1}. Animals were killed by injection of potassium chloride into the LA catheter during general anaesthesia when regional myocardial function had completely recovered after the last ischaemic episode. The heart was dissected and three tissue samples were obtained from the LAD-perfused left ventricle in each dog. LAD samples were taken from the immediate vicinity of the wall-thickening probes. Only samples from animals with severe ischaemic dysfunction, as determined by the wall-thickening probe, were included (no animal was excluded due to insufficient dysfunction). Samples were further dissected into the subendocardial, subepicardial, and mid-myocardial layers. Measurement of microspheres in the tissue samples was performed as described previously.[7] Measurement of regional myocardial blood flow to the regions described was carried out four times during the experiment, as follows: (1) without naloxone and without ischaemia (control), (2) without naloxone during ischaemia, (3) after naloxone and without ischaemia, and (4) after naloxone and during ischaemia.

Experiments were conducted in chronically instrumented conscious dogs to avoid the effects of acute surgical trauma, anaesthesia, volume and ionic imbalances, and temperature on recovery from stunning. As multiple stun manoeuvres may induce extensive development of coronary collaterals thus precluding the induction of post-ischaemic dysfunction, the number of ischaemic episodes was restricted to two in each animal.

Statistical analysis

Data were analysed using repeated-measures two-way ANOVA followed by Bonferroni-corrected Student's *t*-test as appropriate; $P<0.05$ was considered significant. Data are presented here as mean plus or minus standard error of the mean (SD).

Results

None of the animals was excluded from the analysis due to insufficient dysfunction. The maximum degree of regional ischaemic dysfunction was similar during the first and the second ischaemic episodes in each dog.

ANP and BNP levels

Regional myocardial ischaemia in the LAD-perfused area caused a significant release of ANP (Fig. 1A) only in the control without naloxone (peak levels: 182 (SD 30) *vs* 29 (7) pg ml^{-1} at BL). Between 1 and 180 min of reperfusion, ANP levels were significantly higher in the control ($P<0.05$) as compared with the experiment with naloxone pre-treatment. After naloxone pre-treatment, ANP levels remained unchanged during and after regional ischaemia. Myocardial BNP (Fig. 1B) release during regional ischaemia and reperfusion was not different between experiments with or without naloxone.

Arterial blood pressure, left atrial pressure, heart rate, LV dP·dt$_{max}$$^{-1}$, and LV dP·dt$_{min}$$^{-1}$

There were no significant changes in arterial pressure in either experimental group during or after ischaemia (Table 1). Left atrial pressure during LAD ischaemia increased significantly only in the control. Induction of regional ischaemia did not induce a significant alteration of LV dP·dt$_{max}$$^{-1}$ (Table 1) in the control. After naloxone pre-treatment, LV dP·dt$_{max}$$^{-1}$ was significantly elevated during ischaemia and remained so until 30 min of reperfusion. After naloxone, LV dP·dt$_{min}$$^{-1}$ was significantly lower during ischaemia and remained so until 720 min of reperfusion, as compared with the control experiments (Table 1). Heart rate during LAD ischaemia increased significantly in both experiments, but there was no significant difference between the two experiments during or after ischaemia.

Blood flow velocity in the LAD artery

During LAD occlusion, LAD flow velocity decreased to zero and increased to significantly higher values compared with the BL for the first 15 min during reperfusion (Table 1). There were no statistically significant differences between the experimental groups in blood flow velocity in the LAD-perfused area.

Regional myocardial wall thickening

In all animals, severe regional myocardial dysfunction occurred during LAD occlusion. Induction of regional ischaemia led to a significant reduction in WTF to negative values ('wall thinning') in both experimental conditions (Fig. 2). During ischaemia, WTF in the LAD-perfused area expressed as a percentage of the BL value was reduced to –56 (13)% in the experiment with naloxone and to –58 (14)% in the experiment without naloxone. During reperfusion, WTF in relation to pre-ischaemic BL recovered significantly faster with naloxone as compared without naloxone at time points between 1 and 30 min of reperfusion (94 (10) *vs* 23 (39)% at 1 min; 99 (7) *vs* 33 (48)% at 5 min; 98 (6) *vs* 40 (50)% at 15 min; 94 (12) *vs* 47 (36)% at 20 min; and 92 (9) *vs* 49 (29)% at 30 min). After 30 min of reperfusion no significant difference in WTF occurred. BL WTF values were reached after 48 h of reperfusion with and without naloxone.

Regional myocardial blood flow

During LAD occlusion, sub-endocardial blood flow decreased significantly from 0.74 (0.24) to 0.08 (0.01) ml g^{-1} min^{-1} without ($P<0.05$ *vs* BL), and from 1.1 (0.19) to 0.1 (0.05) ml g^{-1} min^{-1} with naloxone ($P<0.05$ *vs* BL). Administration of naloxone in the absence of ischaemia led to a significant increase in sub-endocardial blood flow to the LAD-perfused areas (0.74 (0.24) *vs* 1.1 (0.19) ml g^{-1}

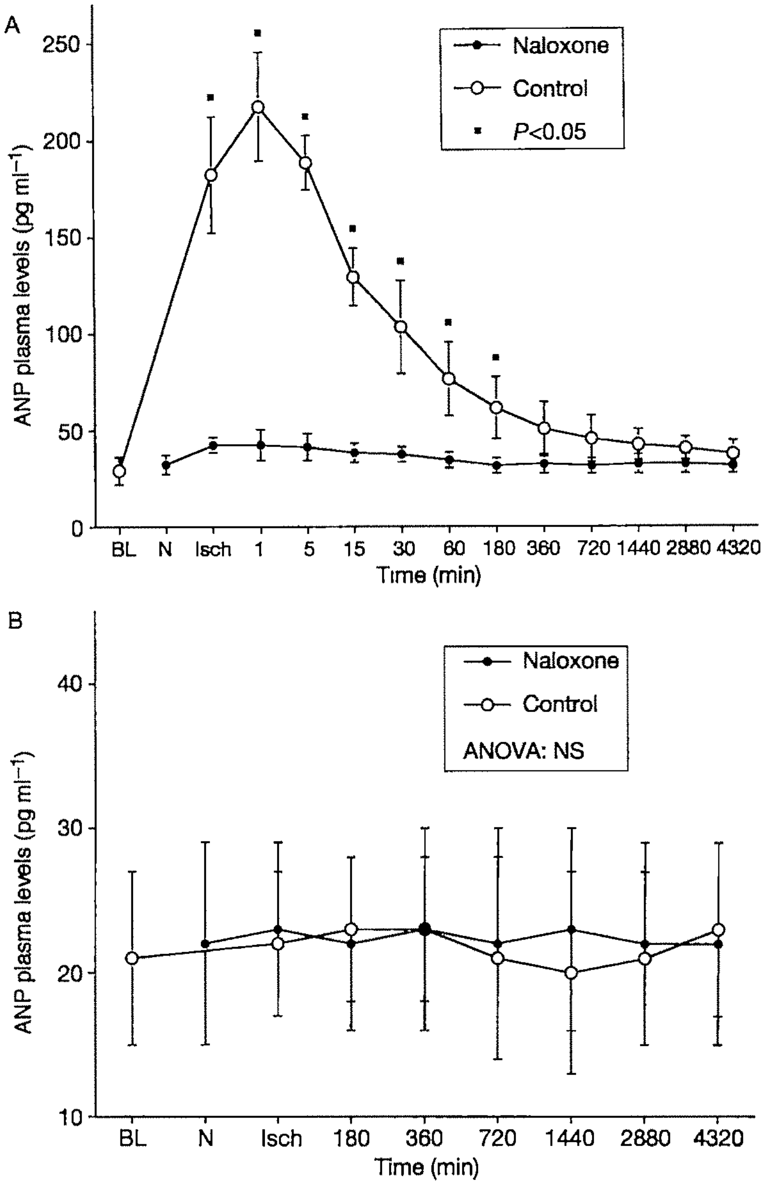

Fig 1 ANP and BNP plasma levels at BL, after pre-treatment with naloxone (Nalox), and during the reperfusion period in pg ml^{-1}. Data are presented as mean±SD and P-values refer to between the group difference. Significant compared with the corresponding BL values or not significant (NS). Isch, ischaemia (10 min); N, naloxone

min^{-1}). Without ischaemia, naloxone caused a significant increase in the blood flow ratio between the sub-endocardial and the sub-epicardial regions (endocardial/epicardial ratio) in the LAD-perfused area (1.2 (0.74) *vs* 2.21 (1.04)). Blood flow ratio to the sub-endocardial layers between the occluded (LAD-perfused area) and the normal, non-ischaemic zone (occluded/normal ratio) during ischaemia was not different with and without naloxone.

Discussion

In this chronically instrumented dog model ANP levels increased significantly during regional LAD ischaemia and remained elevated during myocardial stunning. Pre-ischaemic administration of naloxone completely prevented this increased ANP release. Myocardial BNP release during regional ischaemia and reperfusion was not different with or without naloxone.

Plasma concentrations of the cardiac natriuretic peptides ANP and BNP may be of prognostic value for risk stratification after myocardial infarction.[1] ANP is released from granules in atrial myocytes during atrial stretch, whereas BNP is released from the ventricle. All effects mediated by natriuretic peptides, for example inhibition of sympathetic stimulation of the heart, serve to reduce arterial and venous pressures, and blood volume. They are similarly upregulated in heart failure, whereas BNP seems to be superior in detecting myocardial cell damage.[1] In our

Table 1 Arterial blood pressure (ABP), left atrial pressure (LAP), rate of increase in left ventricular pressure (LV dP·dt$_{max}^{-1}$), rate of decrease in left ventricular pressure (LV dP·dt$_{min}^{-1}$), heart rate (HR), and blood flow velocity in the left anterior descending coronary artery (BFV LAD) for the control group and naloxone groups at BL, during ischaemia, and at predetermined time points during reperfusion Data are presented as mean values (SD). *Significant as compared with BL Significant as compared with control

Variable	Experiment	BL	Ischaemia (5 min after occlusion)	Reperfusion 1 min	5 min	15 min	30 min	60 min	180 min	360 min	720 min	1440 min	2880 min	4320 min
ABP (mm Hg)	Control	125 (34)	121 (22)	124 (25)	123 (21)	122 (13)	125 (23)	122 (32)	124 (29)	125 (36)	122 (43)	123 (33)	125 (45)	124 (39)
	Naloxone	126 (33)	123 (28)	127 (47)	124 (45)	126 (38)	121 (36)	118 (51)	123 (47)	122 (42)	124 (39)	125 (29)	121 (38)	119 (52)
LAP (mm Hg)	Control	2.7 (5)	8 6 (10)*	3.4 (6)	2 9 (7)	2.3 (8)	2 4 (3)	2 7 (5)	2.1 (6)	2.5 (3)	2 2 (4)	2.4 (5)	2.5 (6)	2 3 (2)
	Naloxone	2.3 (7)	5.2 (8)	2.7 (3)	2 1 (5)	2.5 (4)	2 2 (2)	2 5 (3)	2.3 (2)	2 6 (6)	2 8 (1)	2 7 (2)	1 9 (4)	2 0 (3)
LV dP dt_{max}^{-1} (mm Hg s^{-1})	Control	1231 (698)	1162 (595)	1189 (688)	1206 (598)	1196 (621)	1223 (567)	1263 (872)	1168 (881)	1253 (984)	1236 (768)	1187 (1093)	1225 (761)	1250 (981)
	Naloxone	1404 (967)	1687 (896)	1647 (652)	1563 (483)	1686 (497)	1644 (625)	1445 (983)	1369 (766)	1412 (1014)	1384 (885)	1364 (651)	1379 (512)	1428 (782)
LV dP·dt_{min}^{-1} (mm Hg s^{-1})	Control	−631 (437)	−513 (353)	−539 (411)	−547 (475)	−551 (393)	−558 (455)	−567 (421)	−569 (396)	−579 (368)	−581 (659)	−623 (465)	−674 (397)	−652 (426)
	Naloxone	−795 (506)	−1331 (391)*	−1392 (447)*	−1324 (518)*	−1367 (489)*	−1327 (557)*	−1282 (618)*	−1247 (452)*	−1173 (637)	−1009 (742)	−853 (612)	−794 (584)	−884 (565)
HR (beats min^{-1})	Control	87 (15)	110 (21)*	117 (11)*	99 (27)	95 (19)	97 (38)	96 (26)	86 (41)	85 (19)	87 (19)	91 (39)	92 (31)	83 (29)
	Naloxone	90 (13)	112 (13)*	114 (27)*	110 (31)	91 (24)	88 (37)	87 (31)	94 (32)	89 (35)	90 (27)	93 (34)	85 (26)	86 (31)
BFV LAD (kHz)	Control	5.9 (4.2)	0*	12.6 (10.3)*	11 2 (6.9)*	8.9 (7.4)*	6 7 (3 9)	6 3 (3.6)	5 8 (3.8)	6 1 (3.4)	5 9 (3 1)	5 4 (4.4)	5.4 (3 3)	5.5 (3.7)
	Naloxone	5 6 (3.6)	0*	11.4 (10 9)*	11 7 (8 1)*	9 2 (6.7)*	6 4 (4 1)	5.9 (3.9)	5 9 (4 4)	5 5 (3.8)	6 3 (4.2)	6 0 (2 8)	5.5 (2.9)	5.9 (3.1)

investigation, ANP increased 6-fold during regional ischaemia and 7- to 8-fold in the first minute of reperfusion during myocardial stunning. Furthermore, the decreasing ANP levels over time correlated with the increased recovery of stunning. Peak ANP levels are, therefore, possibly useful in assessing the severity of myocardial stunning, especially in the absence of an elevated BNP release over time. They may also help to distinguish between stunning and post-infarction left ventricular dysfunction, because an elevated BNP release would be expected with myocardial infarction but not with myocardial stunning *per se*.[8 9] Furthermore, in our investigation the 10 min of coronary artery occlusion did not induce an increase for myocardial BNP release, even after 3 days of reperfusion. This supports our stunning model, and the hypothesis that isolated increased ANP levels are strongly correlated with myocardial stunning in the absence of necrosis.

Previously, we demonstrated that naloxone improved functional recovery of myocardial stunning and the ischaemic and post-ischaemic systolic left ventricular performance in conscious dogs through its action on the central nervous system.[3] EOPs are found in central areas near the cardiovascular centres of the brain, in the hypothalamus, and peripherally in the myocardium.[10] Naloxone exerts central and peripheral effects on the heart tissue itself.[11] However, the above described protective effects of naloxone[3] are probably, in the main, mediated by its antagonistic action at central opioid receptors.[12] The opioid receptor antagonist naloxone methylbromide, which unlike naloxone does not cross the blood–brain barrier, did not improve myocardial stunning in conscious dogs.[3] Central effects of naloxone are, therefore, predominant, mainly on the hypothalamus.[13] However, the central sites at which naloxone exerts this action have not been determined. EOPs, released upon myocardial ischaemia,[4] activate all central opioid receptors (μ, δ, κ). This activation leads to sympathoinhibition and contributes to negative inotropic effects on the myocardium. Experimental data suggest that the increased endogenous opioids during heart failure act mainly on the δ-receptors[13] and κ-receptors.[15] Activation of these receptors decreases myocardial mechanical performance and alters regional blood flow distribution. Suggestions exist that the effects of non-opioid sigma receptor ligands are mediated via two receptor subtypes, of which one is positive and the other is negative inotropic.[16] From current knowledge it is unclear which effect is predominant. Pharmacological studies led to the proposal that myocardial ε receptors do not play an important role, at least on cardiac rhythm.[17] In contrast, anti-arrhythmic effects mediated by δ-,[18] μ-, κ-receptor agonists, and σ-receptor mediated proarrhythmic effects are described.[17] The σ opioid receptor has been demonstrated to play a major role in cardiac protection in acute instrumented animals[19 20] or isolated organs and in relation to ischaemic preconditioning.[21] In our experiments, performed in chronically instrumented dogs, the antagonistic effects of naloxone dominate. Also, we did

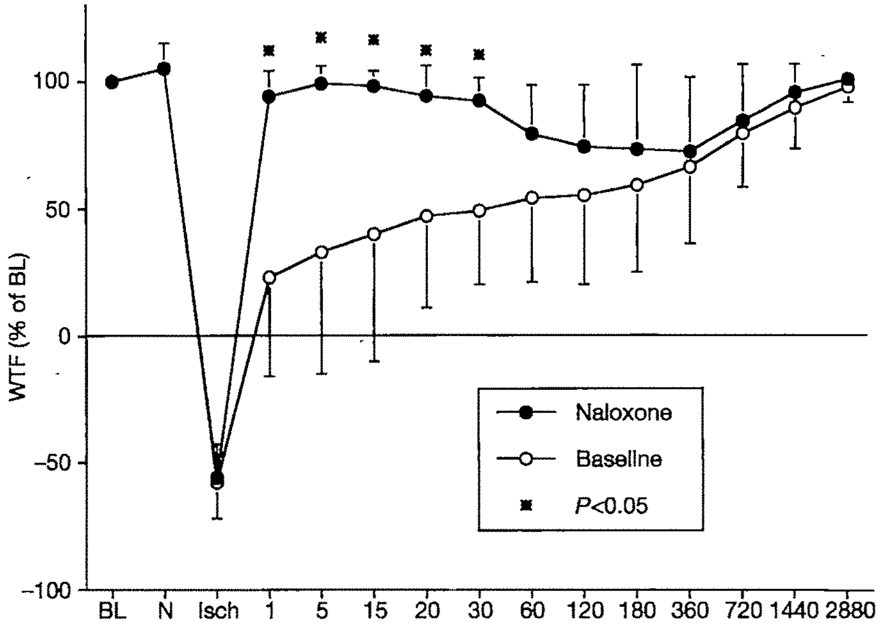

Fig 2 WTF of the area perfused by the LAD coronary artery as a percentage of control values during the reperfusion period Data are presented as mean±SD and *P*-values refer to between the group difference Significant compared with the corresponding BL values. Isch, ischaemia (10 min), N, naloxone.

not use ischaemic preconditioning before the ischaemic episode. Therefore, the different results may only reflect the different experimental settings. Acute instrumentation induces myocardial damage due to massive sympathetic stimulation and σ opioid agonism mediates cardioprotective effects during acute surgical stress. This is not inevitably at variance to our results. Nevertheless, selective opioid receptor block might provide a starting-point for effectively treating the negative inotropic effects of myocardial stunning. However, further investigations in this area will be needed.

Naloxone not only improved systolic function, but also left ventricular diastolic function during regional ischaemia and myocardial stunning. Naloxone also prevented a significant left atrial pressure increase and improved endocardial blood flow during ischaemia. These improvements explain, at least in part, the absence of an increased ANP release during ischaemia and myocardial stunning with naloxone pre-treatment. The absent ANP release, therefore, reflects the positive effects of naloxone on ischaemic and post-ischaemic myocardial dysfunction. No cardiovascular effects of naloxone alone, or a direct inhibitory effect on ANP secretion were found under BL conditions.

This study has some limitations. First, the results obtained are restricted to dogs; there may be relevant species differences in severity and duration of the ischaemic response and its modulation by naloxone. Secondly, the study design does not allow any conclusion of possible mechanisms of the observed effect. Thirdly, a dose–response relationship regarding the protective effect of naloxone was not established.

In conclusion, ANP release, in contrast to BNP release, is enhanced during regional myocardial ischaemia and stunning in conscious dogs. Naloxone completely prevents this increased ANP release. This study is the first description showing that ANP is part of the neurohumoral profile that occurs during myocardial stunning.

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Concurrent ketamine and alfentanil administration: pharmacokinetic considerations

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Background. A ketamine–alfentanil combination has been suggested for total i.v. anaesthesia. We determined the pharmacokinetics of ketamine and alfentanil, alone and together, in three groups of adult male rats, to assess any pharmacokinetic interaction.

Methods. Group 1 animals were infused with i.v. ketamine for 5 min; in group 2, constant low plasma concentrations of alfentanil were maintained by computer-controlled infusion; in group 3, the treatments were combined. Serial plasma and terminal tissue concentrations were measured by high performance liquid chromatography or gas chromatography-mass spectrometry.

Results. In the presence of alfentanil, the mean plasma ketamine concentration–time area under the curve (AUC) value was significantly lower (by 13%, $P<0.05$), while clearance (Cl_T) and volume of distribution (V_{SS}) were significantly higher (by 16 and 28%, respectively, both $P<0.05$). Tissue:plasma distribution coefficients for ketamine in the presence of alfentanil were significantly higher in forebrain (by 128%, $P<0.005$), hindbrain (by 207%, $P<0.01$), gut (by 254%, $P<0.005$), and fat (by 344%, $P<0.0001$). Mean AUC values for alfentanil did not differ significantly in the presence of ketamine, but alfentanil tissue concentrations were significantly lower in forebrain (by 77%, $P<0.0001$), hindbrain (by 28%, $P<0.01$), heart (by 33%, $P<0.01$), lung (30%, $P<0.05$), and gut (by 21%, $P<0.05$). Corresponding tissue:plasma distribution coefficients were significantly lower for forebrain (by 69%, $P<0.0001$) alone.

Conclusions. The finding that the distribution of ketamine into the brain was increased by low plasma concentrations of alfentanil could have important clinical applications for pain management.

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Keywords: anaesthetics i.v., ketamine; analgesics opioid, alfentanil; pharmacokinetics, tissue uptake; pain, management; rat

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The convenience and benefits of total intravenous anaesthesia (TIVA) with drugs having rapid onset and short duration of action makes it an appealing method for surgical procedures where close control of response, along with rapid and lucid recovery, is required, especially being useful for day case surgery. At the same time, multi-modal drug treatment to manage consciousness and nociception has been progressively finding its way into TIVA. It has been suggested recently that alfentanil is a useful adjunct to ketamine anaesthesia by providing essential haemodynamic stability[1] and that ketamine may antagonize hypoventilation caused by alfentanil.[2] Although a ketamine–alfentanil combination may provide an excellent basis for TIVA, as yet, it has not been determined whether there is any pharmacokinetic interaction between these agents.

This study was designed to determine the whole body pharmacokinetics and tissue distribution of ketamine and of its pharmacologically active metabolite, norketamine, when administered alone and in the presence of constant low-level plasma alfentanil concentrations, in rats.

Materials and methods

Animals and techniques

This study was approved by the Animal Care and Ethics Committee of the Royal North Shore Hospital. Adult male Wistar rats (350–400 g, obtained from the Gore Hill Research Laboratories, Sydney, Australia) were used. The animals were housed in sets of four, on a constant 12/12 h

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light/dark cycle at 21°C, with free access to food and water until the time of surgery; after surgery they were housed individually. Chronic indwelling cannulae were implanted into the jugular vein and carotid artery to allow simultaneous venous infusion of drug solutions and sampling of arterial blood as described previously.[3]

Drugs

Ketamine hydrochloride (Ketalar™, Parke-Davis Australia Pty Ltd, Sydney, Australia) was diluted to a concentration of 20 mg ml^{-1} (17.3 mg ml^{-1} as base); alfentanil hydrochloride (Rapifen™, Astra-Zeneca Australia Pty Ltd, Sydney, Australia) was diluted to a concentration of 100 μg ml^{-1} (92 μg ml^{-1} as base). Both drug solutions were diluted with de-ionized water; alfentanil contained 5 units ml^{-1} heparin.

Experimental design

Studies were performed in three groups of animals 24 h after cannulation, and were carried out between 14:00 and 19:00 h. Infusion and sampling lines (75 and 45 cm, respectively) were attached to the venous and arterial indwelling cannulae, and the animals were placed in a study chamber and allowed to settle for 30 min before commencement of the study. The relevant drug infusions (see below) were delivered by a syringe driver (Harvard Apparatus, Model 22) from a gas tight syringe (Hamilton, 5 ml). In groups 1 and 3 (described below), immediately after loss of righting reflex, the animals were removed from the study chamber, a rectal thermal probe was inserted, and body temperature was maintained by a heating lamp; no loss of righting reflex occurred in group 2. Once motor function began to return the rectal probe was removed and the animals were returned to the study chamber. Arterial blood samples (100 μl) were collected into heparinized (50 units) 1.5 ml polyethylene microfuge tubes for drug analysis; these were replaced with 3 volumes of 0.9% saline as described previously.[3] After the final blood sample was collected, the animals were killed by carbon dioxide asphyxiation. Central nervous system (CNS=regional brain and spinal cord), heart, lung, liver, kidney, gut, adductor muscle, and epididymal fat pad tissues were sampled for the determination of tissue:plasma drug distribution. The tissue: plasma distribution coefficients of ketamine and alfentanil were determined after each of the following infusion paradigms.

Group 1. An infusion of ketamine was administered at a constant rate of 10 mg kg^{-1} min^{-1} over 5 min; serial arterial blood samples were taken before, then at 1.5, 3, 5, 7, 10, 15, 20, 30, 40, 60, 80, 100, 120, 140, 160, and 180 min after commencement of the infusion.

Group 2. An infusion of alfentanil, computer-controlled by Stanpump software,[4] was used to maintain a constant plasma concentration of alfentanil (target value of 100 μg ml^{-1}) that would be antinociceptive, without causing significant ventilatory impairment or EEG changes, based on previous animal experiments.[5–8] Pharmacokinetic parameters, describing a three-compartment mamillary model, were obtained from previously published data[9] and used to implement the infusion algorithm. Serial arterial blood samples were collected before, then at 1.5, 3, 5, 10, 20, 40, 60, 80, 100, 120, 140, 160, and 180 min for the duration of the infusion.

Group 3. An infusion of ketamine was administered over 5 min as in group 1, the infusion line for ketamine was then removed and a new infusion line primed with alfentanil was attached; 7 min later (i.e. at 12 min after the start of the ketamine infusion), alfentanil was delivered by the Stanpump infusion paradigm as in group 2. Blood samples were collected as before in group 1: the first blood sample to contain alfentanil was taken at 15 min (i.e. 3 min after commencement of the alfentanil infusion). Ketamine and alfentanil plasma concentrations were measured in the same blood samples.

Analytical procedures

In group 1, concentrations of ketamine and norketamine were measured as the sum of individual R(–)- and S(+)-ketamine enantiomer concentrations determined by HPLC following chiral separation on a micro chiral-AGP column.[10] This method was not suitable for the concurrent determination of ketamine and alfentanil in groups 2 and 3, due to marked differences in their chromatographic characteristics on this column type and inadequate sensitivity for the determination of alfentanil concentrations. In these groups the plasma and tissue concentrations of alfentanil, ketamine, and norketamine were determined by adaptation of previously published gas chromatography-mass spectrometry (GC-MS) procedures,[11 12] as described below.

Plasma. After the addition of cyproheptadine (50 μl, 1 μg ml^{-1}, internal standard) and Na_3PO_4 (100 μl, 0.5 M), aliquots of plasma (50 μl) in polypropylene tubes (1.5 ml) were briefly vortex-mixed, then extracted by shaking (5 min) with cyclohexane containing iso-amyl alcohol (1 ml, 2% $v.v^{-1}$). Tubes were centrifuged (3000 r.p.m., 5 min) and the organic phase transferred to a fresh polypropylene tube (1.5 ml) with a Pasteur pipette, dried in a bench rotatory vacuum centrifuge, reconstituted in toluene (100 μl), and transferred to polypropylene inserts immediately before analysis.

Tissues. Homogenates of tissue (100 mg ml^{-1}) in NaH_2PO_4 (100 mM) were frozen and resuspended after thawing immediately before analysis. Aliquots of homogenate (1 ml) were transferred to polypropylene tubes (10 ml), before the addition of cyproheptadine (100 μl, 1 μg ml^{-1}, internal standard) and NaOH (250 μl, 1 M). The tubes were briefly vortex-mixed, then extracted by shaking (5 min) with cyclohexane containing iso-amyl alcohol (3 ml, 2% $v.v^{-1}$). After centrifugation (3000 r.p.m., 5 min), the organic phase was transferred to a fresh polypropylene tube (10 ml) with a Pasteur pipette, and HCl (400 μl, 0.5 M) was added. Tubes

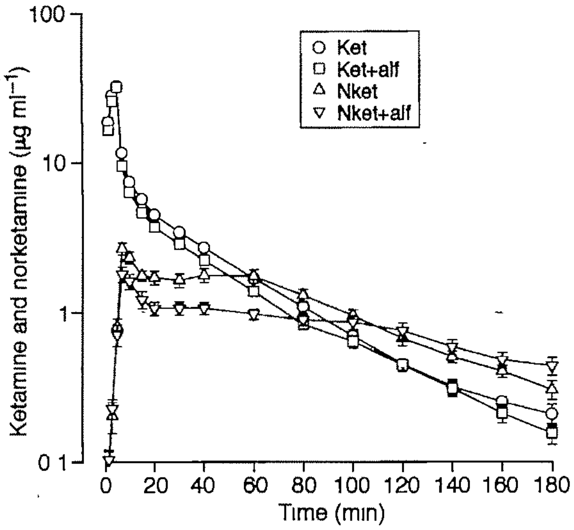

Fig 1 Mean (SEM) plasma ketamine and norketamine concentrations in rats after initial infusion of ketamine at 10 mg kg^{-1} min^{-1} over 5 min, alone (n=9) or when followed 12 min later, by Stanpump-controlled alfentanil infusion (n=8) until conclusion of the study at 180 min.

Table 1 Pharmacokinetic parameters (mean (SEM)) for ketamine following infusion of ketamine alone, at 10 mg kg^{-1} min^{-1} over 5 min, and when followed by Stanpump-controlled alfentanil infusion. Significance (Student's t-test) *$P<0.05$ for ketamine *vs* ketamine with alfentanil Cl_T, mean total body clearance, V_C, apparent initial dilution volume, V_{SS}, steady state apparent volume of distribution; $t_{1/2}$, terminal elimination half-life; MRT, mean residence time

Parameter	**Ketamine (n=9)**	**Ketamine with alfentanil (n=8)**
Cl_T (litre min^{-1})	0.043 (0.001)*	0.050 (0.003)
V_C (litre)	0.15 (0.01)	0.18 (0.01)
V_{SS} (litre)	1.38 (0.08)*	1.76 (0.14)
$t_{1/2}$ (min)	38 (4)	49 (12)
MRT (min)	31 (1)	30 (1)

were shaken (5 min) and centrifuged as before, the organic phase was decanted and discarded, and NaOH (60 µl, 5 M) was added. After brief vortex mixing, cyclohexane containing iso-amyl alcohol (1 ml, 2% $v.v^{-1}$) was added and the tubes shaken and centrifuged as before. The organic phase was transferred to a polypropylene tube (1.5 ml) with a Pasteur pipette, dried in a bench rotatory vacuum centrifuge, reconstituted in toluene (100 µl), and transferred to polypropylene inserts immediately before analysis.

GC-MS methodology. Toluene extracts were analysed on a Hewlett Packard 5972 MS/5890 Group II GC system, operating in electron impact mode (70 eV), after split-less injection onto a capillary column (HP-5MS, 30 m length × 0.25 mm ID, 0.25-µm film thickness). The oven temperature was held at 110°C initially for 0.5 min then increased at 25°C min^{-1} to 280°C, while the injector and transfer lines were maintained at 280°C. Helium was used as the carrier gas at a flow rate of 1 ml min^{-1}. A run time of 10 min and an injection volume of 1 µl were used for the analysis of ketamine and norketamine, while for alfentanil a run time of 15 min and an injection volume of 5 µl was used. Mass fragments (and retention times) for ketamine and norketamine were monitored with a dwell time of 50 ms at m/z 180 (6.1 min) and m/z 166 (6.0 min), respectively; alfentanil and cyproheptadine were monitored with a dwell time of 100 ms at m/z 289 (12.7 min) and m/z 287 (8.2 min), respectively.

Data analysis

Area under the curve (AUC) values for each plasma concentration–time data set were determined by the linear trapezoid method. Distribution coefficients were calculated as the ratio of tissue to plasma analyte concentrations, uncorrected for residual tissue blood volume. Between group comparisons of the tissue distribution coefficients for ketamine and norketamine were performed on log-transformed values, and the antilogs of the mean log-transformed values were subsequently referred to as the log-normalized values of the distribution coefficients. Regional CNS tissue drug concentrations and distribution coefficients were compared by one-way analysis of variance (ANOVA); individual post-hoc comparisons between mean values were performed by the method of Least Significant Difference (Statistix for Windows®, Analytical Software, Tallahassee, FL, USA). Tissue drug concentrations and distribution coefficients between the two infusion paradigms were compared by Student's two sample t-tests. The pharmacokinetic parameters for ketamine were determined by fitting polyexponential decay equations to the concentration–time washout curve, and the mean total body clearance (Cl_T), initial dilution volume (V_C), volume of distribution at steady state (V_{SS}), terminal half-life ($t_{1/2}$), and mean residence time in the body (MRT) were calculated by conventional means.[13] Data are expressed as mean (SEM) unless specified otherwise.

Results

Ketamine and norketamine concentrations in arterial plasma following infusion in groups 1 and 3 are compared in Figure 1. The mean value of ketamine AUC for group 1 (ketamine alone=429 (7) µg min ml^{-1}) was significantly greater (P=0.031) than the value for group 3 (ketamine followed by alfentanil=372 (21) µg min ml^{-1}). Similarly, the mean value of the AUC for norketamine was also significantly greater (P=0.038) in group 1 (199 (16) µg min ml^{-1}) than for group 3 (150 (14) µg min ml^{-1}) due, mainly, to the plasma norketamine concentrations being significantly different (P<0.05) between 7 and 90 min. The pharmacokinetic parameters for ketamine following infusions in groups 1 and 3 are given in Table 1. Both clearance (Cl_T) and volume of distribution at steady state (V_{SS}) were significantly greater for ketamine when the alfentanil infusion followed the ketamine infusion ($P<0.05$).

Ketamine tissue concentrations and distribution coefficients at the conclusion of serial blood sampling in groups 1 and 3 are shown in Tables 2 and 3. Regional differences in CNS ketamine concentrations were not significant in group 1 but were apparent in group 3 ($F_{2,21}=6.78$, $P=0.005$; hindbrain > spinal cord: $P=0.025$; hindbrain > forebrain: $P=0.002$). Similarly, there were significant differences in regional CNS norketamine concentrations in group 3 ($F_{2,21}=4.27$, $P=0.028$; hindbrain > forebrain: $P=0.02$). In group 1, norketamine enantiomer concentrations in the CNS and myocardium were lower than the limit of (spectrophotometric) quantitation following HPLC-chiral separation. Ketamine CNS tissue concentrations were significantly higher in forebrain ($P<0.05$) and hindbrain ($P<0.01$) following infusions in group 3 than in group 1; the corresponding log-transformed distribution coefficients were also significantly higher for forebrain ($P<0.005$) and hindbrain ($P<0.01$). Log-transformed CNS distribution coefficients for ketamine in group 1 did not differ regionally. In group 3, significant regional CNS differences were apparent for ketamine ($F_{2,21}=4.99$, $P=0.017$; hindbrain > forebrain: $P=0.01$), but not norketamine.

Ketamine concentrations in the lungs were significantly lower in group 3 than in group 1 ($P<0.05$), but those in the gut ($P<0.05$) and fat ($P<0.001$) were significantly higher; the corresponding log-transformed distribution coefficients were also significantly lower in the lungs ($P<0.05$) and significantly higher in gut ($P<0.005$) and fat ($P<0.001$). Norketamine concentrations were significantly higher in liver ($P<0.001$), kidney ($P<0.005$), gut ($P<0.001$), and fat ($P<0.001$) following infusions in group 3, than in group 1, but the corresponding log-transformed distribution coefficients for these tissues were not significantly different.

Alfentanil arterial plasma concentrations from the Stanpump-controlled infusions in group 2 and 3 animals are shown in Figure 2. In group 2 animals, where alfentanil infusion was given alone, the animals displayed episodic sleep-like behaviour, but did not demonstrate other potential alfentanil-induced effects such as loss of righting reflex, ataxia, increased muscle tone, or convulsions. The mean AUC value from 20 to 180 min for alfentanil was not significantly different between the infusions in group 2

Table 2 Mean (SEM) ketamine (Ket) and norketamine (Nket) plasma and tissue concentrations in rats after initial infusion of ketamine at 10 mg kg^{-1} min^{-1} over 5 min, alone or when followed 12 min later, by Stanpump-controlled alfentanil (Alf) infusion until conclusion of the study at 180 min Sample numbers are given in square parentheses [*n*] Significance (Student's *t*-test) is given by superscripts: Ket *vs* Ket+Alf and Nket *vs* Nket+Alf. $^{*}P<0.05$; $^{+}P<0.01$, $^{\dagger}P<0.005$, $^{\ddagger}P<0.001$; na=not available

Concentration	Ket (n=9)	Ket+Alf (n=8)	Nket (n=9)	Nket+Alf (n=8)
Final plasma (μg ml^{-1})	0.22 (0.04) [8]	0.16 (0.02)	0.33 (0.04) [8]	0.44 (0.06)
CNS tissue (μg g^{-1})				
Forebrain	0.6 (0.1)	1.0 (0.1)*	na	0.6 (0.1)
Hindbrain	0.9 (0.2)	1.9 (0.3)$^{+}$	na	0.9 (0.1)
Spinal cord	1.7 (0.6)	1.2 (0.2)	na	0.7 (0.1)
Peripheral tissue (μg g^{-1})				
Liver	0.9 (0.3)	0.6 (0.1)	5.4 (0.5)	11.2 (2.0)*
Kidney	36.9 (2.4)	35.4 (2.7)	32.4 (2.8)	54.0 (5.1)†
Heart	3.8 (1.5)	0.6 (0.1)	na	0.7 (0.1)
Lung	7.2 (2.7)	0.5 (0.2)*	0.7 (0.2)	1.2 (0.2)
Gut	1.0 (0.1)	2.9 (0.7)*	29.1 (2.1)	61.6 (9.7)*
Muscle	na	0.9 (0.2)	na	1.0 (0.1)
Fat	3.7 (0.4)	12.1 (1.5)‡	0.4 (0.1)	1.0 (0.3)*

Table 3 Log-normalized mean (and 95% confidence limits) tissue.plasma distribution coefficients (uncorrected for residual blood volume) for ketamine (Ket) and norketamine (Nket) in rats after initial infusion of ketamine at 10 mg kg^{-1} min^{-1} over 5 min, alone or when followed 12 min later, by Stanpump-controlled alfentanil (Alf) infusion until conclusion of the study at 180 min Sample numbers are given in parentheses (*n*) Significance (Student's *t*-test) is given by superscripts· Ket *vs* Ket+Alf and Nket *vs* Nket+Alf. $^{*}P<0.05$; $^{+}P<0.01$, $^{\dagger}P<0.005$, $^{\ddagger}P<0.0001$; na=not available

Distribution coefficient	Ket (n=8)	Ket+Alf (n=8)	Nket (n=8)	Nket+Alf (n=8)
CNS tissue				
Forebrain	2.8 (2.0–4.1)	6.4 (5.0–8.2)†	na	1.4 (1.1–2.1)
Hindbrain	3.9 (2.1–7.0)	12 (9.0–17)$^{+}$	na	2.1 (1.6–3.0)
Spinal cord	5.6 (2.3–14)	8.1 (6.0–10.9)	na	1.6 (1.2–2.3)
Peripheral tissue				
Liver (ket n=7)	3.7 (1.4–9.5)	3.5 (2.5–5.0)	18 (14–21)	27 (19–44)
Kidney	182 (138–239)	240 (174–330)	104 (83–129)	134 (100–202)
Heart	9.6 (3.1–30)	4.2 (3.3–5.4)	na	1.5 (1.2–2.1)
Lung (ket+Nket n=6)	28.5 (7.8–104)	2.9 (1.8–4.8)*	2.3 (1.0–5.2)	2.6 (2.0–3.9)
Gut	4.6 (3.0–7.1)	16.3 (11–25)†	93 (71–121)	135 (99–209)
Muscle	na	5.5 (4.3–7.2)	na	2.1 (1.6–3.1)
Fat	18 (13–24)	80 (64–101)‡	1.1 (0.8–1.7)	1.8 (1.0–4.0)

(7625 (134) ng min ml^{-1}) and group 3 (7194 (634) ng min ml^{-1}), but plasma alfentanil concentrations were significantly lower (P=0.0012) at 20 min in group 3. Tissue concentrations of alfentanil at 180 min following infusions in groups 2 and 3 are shown in Table 4. Significant regional differences in CNS alfentanil concentrations were apparent in both group 2 ($F_{2,21}$=22.76, P<0.0001; forebrain > hindbrain and spinal cord: P=0.001) and group 3 ($F_{2,21}$=6.48, P=0.0064; forebrain < hindbrain and spinal cord: P=0.02). Concentrations of alfentanil were significantly lower in forebrain (P<0.0001) and hindbrain (P<0.01), when alfentanil infusion followed ketamine administration. Similarly, there were significant differences in the corresponding regional CNS distribution coefficients following alfentanil infusions in both group 2 ($F_{2,21}$=19.28, P<0.0001; forebrain > hindbrain and spinal cord: P=0.001) and group 3 ($F_{2,21}$=4.45, P=0.024; forebrain < hindbrain and spinal cord: P=0.05). Alfentanil distribution coefficient for the forebrain was significantly lower (P<0.0001) when alfentanil infusion followed ketamine administration. Although concentrations of alfentanil were significantly lower in heart (P<0.01), lung (P<0.0001), and gut (P<0.0001) following infusions in group 3, the corresponding distribution coefficients did not differ significantly.

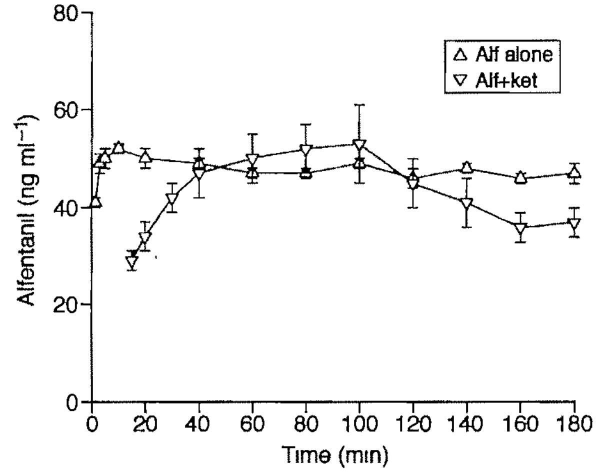

Fig 2 Mean (SEM) plasma alfentanil concentrations in rats during Stanpump-controlled alfentanil infusion alone (n=8), or 12 min after an infusion of ketamine at 10 mg kg^{-1} min^{-1} over 5 min (n=8).

Discussion

Ketamine, a phencyclidine (PCP) analogue, acts as a non-competitive inhibitor of the N-methyl-D-aspartate (NMDA) receptor in the CNS by binding to the PCP recognition site in the NMDA receptor ion-channel complex.[14] Analgesic effects associated with subanaesthetic doses of ketamine appear to be mediated by this non-opioid PCP receptor mechanism in both experimental and postoperative pain.[15 16] Additionally, laboratory studies have found the primary metabolite of ketamine, norketamine, also to have antinociceptive properties,[17] potentially augmenting those of the parent drug. Furthermore, both ketamine and norketamine have been found to inhibit NMDA receptor function stereoselectively.[18]

Alfentanil has a very short duration of action following a brief duration of infusion, mainly due to its weak tissue binding.[19] Although there is evidence for alfentanil to exert a longer half-life and duration of effect with longer durations of infusion,[20–22] it is well-suited to i.v. infusion delivery, especially for intraoperative analgesia in surgical patients. Opioids such as alfentanil reproducibly modify the quantitative electroencephalogram (EEG), especially in the delta (0.5–4.5 Hz) frequency band. Alfentanil plasma concentrations used in the present study were in the range reported as having little to no direct EEG effect. Other studies on antinociceptive effects of alfentanil have found an EC_{50} of 24 ng ml^{-1} for suppression of tooth pulp evoked potential (TPEP) changes in the EEG.[8] Thus, the present study used alfentanil plasma concentrations within the antinociceptive range, but lower than values associated with

Table 4 Mean (SEM) tissue alfentanil (Alf) concentrations and tissue plasma distribution coefficients in rats following Stanpump-controlled alfentanil infusion alone, over 180 min, or 12 min following an infusion of ketamine (Ket) at 10 mg kg^{-1} min^{-1} over 5 min. Sample numbers are given in square parentheses [n]. Significance (Student's t-test) is given by superscripts: Alf *vs* Alf+Ket (Student's t-test) $^{*}P$<0.05, ^{+}P<0.01, $^{\dagger}P$<0.0001

Tissue	Concentration (n=8)		Distribution coefficients (n=8)	
	Alf	Alf+Ket	Alf	Alf+Ket
Final plasma (ng ml^{-1})	47 (2)	37 (3)*		
CNS tissue (ng g^{-1})				
Forebrain	57 (4)	13 (1)†	1.22 (0.10)	0.38 (0.04)†
Hindbrain	32 (2)	23 (2)$^{+}$	0.69 (0.02)	0.66 (0.10)
Spinal cord	33 (3)	25 (3)	0.71 (0.06)	0.71 (0.10)
Peripheral tissue (ng g^{-1})				
Liver	100 (8)	87 (10)	2.17 (0.23)	2.69 (0.68)
Kidney	78 (7)	82 (7)	1.68 (0.16)	2.41 (0.40)
Heart	42 (3)	28 (3)$^{+}$	0.90 (0.06)	0.84 (0.14)
Lung	86 (6)	60 (9)*	1.86 (0.17)	1.78 (0.37)
Gut	71 (4)	56 (5) [7]*	1.52 (0.11)	1.70 (0.34) [7]
Muscle	25 (3)	20 (3)	0.53 (0.06)	0.61 (0.15)
Fat	95 (11)	93 (19)	2.02 (0.22)	2.78 (0.76)

significant direct EEG changes (EC_{50} approximately 200 ng ml^{-1}).[5 7]

Mean values for ketamine Cl_T and V_{SS} (Table 1) were consistent with values reported by others;[23] however, the significantly lower plasma ketamine concentration–time AUC values for group 3 compared with group 1 animals reflect the greater Cl_T and V_{SS} for ketamine during alfentanil infusion. Arterial blood pH and $P\text{CO}_2$ were not measured in this study but, for several reasons, we believe that a ventilatory depressant effect of alfentanil was unlikely to account for this difference. There were no obvious effects of alfentanil in animals when alfentanil infusions were given alone. Plasma alfentanil concentrations less than 100 ng ml^{-1} have previously been shown to have no effect on arterial $P\text{CO}_2$.[8] Moreover, as the pKa of ketamine is 7.5,[24] a decreased arterial blood pH due to ventilatory depression would increase the ionized state fraction of ketamine, thereby retarding its extravascular distribution and resulting in lower values for V_{SS} and possibly Cl_T. Similarly, cardiovascular differences between the two groups are also unlikely to account for the different pharmacokinetic values for ketamine in the presence of alfentanil. Attenuation by alfentanil of ketamine's sympathomimetic-cardiovascular effects could also be expected to retard distribution and reduce V_{SS} and possibly Cl_T. Both the V_{SS} and Cl_T of ketamine; however, were significantly increased in the presence of alfentanil.

Alfentanil appeared to facilitate the uptake of ketamine into both gut and adipose tissue. Opioids tend to reduce sympathetic tone and enhance parasympathetic tone. These effects, along with a possible direct vascular effect, can result in dilation of arterial and venous vascular beds,[25] and possibly account for the greater uptake into gut and adipose tissue, and the higher clearance, found for ketamine in the presence of alfentanil infusion. In the lung, however, tissue uptake of ketamine was less suggesting that, following i.v. infusion of alfentanil, high local concentrations of alfentanil may have displaced ketamine from tissue binding sites. This suggestion is consistent with the known higher affinity of alfentanil than ketamine for plasma proteins,[23] the high degree of ketamine uptake into the lungs,[26] and saturability of binding of such basic drugs in lung tissue.[27]

Tissue norketamine concentrations were significantly higher in liver (52%), kidney (40%), and gut (53%), when ketamine infusion was followed by alfentanil. The lack of significant difference in the corresponding distribution coefficients for norketamine in these tissues most likely reflects significant local metabolism of ketamine to norketamine in these tissues.[10] Significantly higher concentrations of norketamine in adipose tissue, however, probably reflects redistribution from the gut, as local metabolic conversion of ketamine to norketamine would be unlikely. However, the mean AUC value for norketamine was significantly higher (by 25%) in group 1 than group 3 due, mainly, to significant divergence in plasma norketamine concentrations from 7 (to 90) min, 2 min after cessation of the ketamine infusion (alfentanil infusions in group 3 did not begin until 12 min after the ketamine infusion had commenced). Norketamine in group 1 samples was quantified by spectrophotometric detection following chiral stationary phase HPLC separation, but in group 3 norketamine was quantified by the more specific technique of mass-selective detection following gas chromatographic separation. Norketamine, after its formation from ketamine by *N*-demethylation, may undergo further oxidative metabolism to 6-hydroxynorketamine.[28] It is possible that such an additional metabolite contributed to the AUC values for plasma norketamine in group 1, because norketamine concentrations in liver, kidney, and gut (the tissues that contributed to circulating norketamine concentrations) were in fact higher in group 3.

Plasma alfentanil concentrations were significantly lower at 20 min when Stanpump-controlled alfentanil infusion followed ketamine infusion. Ketamine concentrations in plasma were three orders of magnitude higher than those of alfentanil, and competitive displacement from plasma protein binding sites may have facilitated tissue uptake in the early stages of the alfentanil infusion.[23] The subsequent redistribution of ketamine into more poorly perfused tissues appeared to offset the initial facilitated tissue uptake of alfentanil following ketamine infusion. Although tissue concentrations of alfentanil were significantly lower in heart, lung, and gut, when alfentanil infusion followed ketamine administration, the distribution coefficients indicated that tissue uptake of alfentanil by these tissues was not affected by ketamine infusion.

In the CNS, tissue uptake of ketamine into both the forebrain and hindbrain was significantly greater in the presence of alfentanil, although ketamine significantly reduced tissue uptake of alfentanil into the forebrain, possibly suggesting local competitive displacement of alfentanil by ketamine from tissue binding sites. Recently, ketamine has been found to exert analgesic effects supraspinally, through activation of inhibitory monoaminergic pathways descending to the spinal cord, and antihyperalgesic effects at the level of the spinal cord through inhibition of NMDA receptor function.[29] Moreover, opioids also exert analgesic effects through activation of monoaminergic pathways that originate in the brain stem and descend to the spinal cord.[30] Plasma alfentanil concentrations of approximately 50 ng ml^{-1}, maintained over the duration of this investigation, were approximately double the EC_{50} found for suppression of TPEP[8] and therefore likely to be associated with analgesia. Others have reported that ketamine allays the development of antinociceptive tolerance to alfentanil.[31] This finding that the distribution of ketamine into the brain was increased by constant low plasma concentrations of alfentanil could therefore have implications for the interpretation of such pharmacological studies and have important clinical applications for pain management.

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REVIEW ARTICLE

Modulation of β-adrenergic receptor subtype activities in perioperative medicine: mechanisms and sites of action

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This review focuses on the mechanisms and sites of action underlying β-adrenergic antagonism in perioperative medicine. A large body of knowledge has recently emerged from basic and clinical research concerning the mechanisms of the life-saving effects of β-adrenergic antagonists (β-AAs) in high-risk cardiac patients. This article re-emphasizes the mechanisms underlying β-adrenergic antagonism and also illuminates novel rationales behind the use of perioperative β-AAs from a biological point of view. Particularly, it delineates new concepts of β-adrenergic signal transduction emerging from transgenic animal models. The role of the different characteristics of various β-AAs is discussed, and evidence will be presented for the selection of one specific agent over another on the basis of individual drug profiles in defined clinical situations. The salutary effects of β-AAs on the cardiovascular system will be described at the cellular and molecular levels. β-AAs exhibit many effects beyond a reduction in heart rate, which are less known by perioperative physicians but equally desirable in the perioperative care of high-risk cardiac patients. These include effects on core components of an anaesthetic regimen, such as analgesia, hypnosis, and memory function. Despite overwhelming evidence of benefit, β-AAs are currently under-utilized in the perioperative period because of concerns of potential adverse effects and toxicity. The effects of acute administration of β-AAs on cardiac function in the compromised patient and strategies to counteract potential adverse effects will be discussed in detail. This may help to overcome barriers to the initiation of perioperative treatment with β-AAs in a larger number of high-risk cardiac patients undergoing surgery.

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Keywords: sympathetic nervous system, adrenergic block; complications, side-effects; heart, heart rate, perioperative; heart, cardioprotection; sympathetic nervous system, beta-adrenergic receptor

Choice of literature

Literature relevant to the topic of the review was identified by literature search of Medline (1966 to March 2001) using 'beta-blocker', 'beta-adrenergic antagonist', 'beta-adrenergic receptor', 'cardioprotection', 'side-effect', 'perioperative' and combinations of these terms as keywords. The reference lists of relevant articles were further reviewed and personal files were searched to identify additional citations.

Clinical uses of perioperative β-adrenergic antagonists

Current clinical uses of β-adrenergic antagonists (β-AAs) include treatment of arterial hypertension, primary and secondary prevention of myocardial infarction in patients with coronary artery disease, treatment of atrial and ventricular arrhythmias, and, most recently, the treatment of the failing heart.[28 29 37 60 111 121 167] β-AAs belong to the group of first-line antihypertensive agents, decreasing

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Table 1 Perioperative administration of atenolol and bisoprolol. *If p o. administration is not feasible in the perioperative period, esmolol, metoprolol or atenolol should be administered i.v to maintain a heart rate of 50–80 beats min^{-1}

	Perioperative atenolol[142] **Major non-cardiac surgery under general anaesthesia with tracheal intubation**	**Perioperative bisoprolol**[173] **Vascular surgery under general or regional anaesthesia**
Patients	With coronary artery disease (CAD) or at least two risk factors for CAD: age ≥65 yr diabetes current smoking hypertension hypercholesterolaemia	With mild to moderate ventricular wall-motion abnormalities as assessed by dobutamine stress echocardiography Concomitant cardiac risk factors >70 yr diabetes angina prior myocardial infarction history of heart failure ventricular arrhythmias limited exercise capacity
Dosing	5–10 mg atenolol i v. every 12 h 30 min before induction immediately after surgery until discharged (i.v or 50–100 mg p.o.* every 12 h)	5–10 mg bisoprolol p o * once a day 1 week before surgery continued for 30 days postoperatively (p o * or nasogastric tube, or metoprolol i.v)
Safety	heart rate >50 beats min^{-1} systolic blood pressure >100 mm Hg cave contraindications· active asthma, high-degree heart block, manifest congestive heart failure, allergies	heart rate >50 beats min^{-1} systolic blood pressure >100 mm Hg cave contraindications. active asthma, high-degree heart block, manifest congestive heart failure, allergies

cardiac death by 30%,[176] and long-term treatment with β-AAs after myocardial infarction reduces total mortality by more than 30%.[74] Decreased elevation of the MB heterodimer of creatine kinase after coronary interventions associated with improved intermediate-term survival was reported in patients with prior β-AA therapy compared with those not on β-AAs.[198] In addition, it has been estimated from crude annualized mortality rates, derived from trials with inhibitors of angiotensin-converting enzyme (ACE) and with β-AA conducted in heart-failure patients, that β-AAs are more than twice as effective as ACE inhibitors in terms of average reduction in mortality.[34 65] Thus, β-AAs are highly potent cardiovascular drugs.

In spite of this overwhelming evidence, β-AAs are underused in current clinical practice, and physicians prescribe β-AAs only to approximately 50% of patients qualifying for this therapy.[21 122 130 242] Notably, medical contraindications do not appear to explain the low use of β-AAs, and it has been speculated that pharmaceutical industry competitiveness may have contributed to it by leading to exaggeration of the side-effects of β-AAs (harmful lipid profile, decreased sexual function, potential for precipitating congestive heart failure, decreased exercise performance).[112 210] The proof of the concept of β-adrenergic antagonism in cardioprotection, however, is now also firmly established in patients with coexisting disease states that were traditionally considered as contraindications. Particularly, patients older than 80 yr with heart failure (ejection fraction less than 20%), non-Q-wave infarction, diabetes or chronic obstructive pulmonary disease have a disproportionate high benefit from postinfarction β-adrenergic antagonism.[74 205] Therefore, anaesthetists should assume the role of primary caregivers and initiate treatment with β-AAs in surgical patients with well-defined indications for β-AAs who are admitted to the hospital without proper treatment.[78 232]

Because gaining control over the autonomous nervous system constitutes a significant part of perioperative medicine,[59 184] β-adrenergic antagonism has been used traditionally to maintain blood pressure and heart rate within baseline values in various perioperative settings. In particular, β-AAs were successfully used to blunt haemodynamic responses to intubation,[44 154] at the time of emergence caused by decreasing anaesthetic depth,[67] and during electroconvulsive therapy.[46 262] High-dose β-AA treatment is used to maintain deliberate hypotensive anaesthesia,[105 219] and has been used most recently to enable multiple-vessel coronary artery bypass grafting (CABG) on the beating heart.[170 152] Esmolol-enriched normothermic blood also resulted in better myocardial protection compared with crystalloid cardioplegia in patients undergoing CABG surgery.[19] In addition, perioperative β-AAs reduce the incidence of atrial fibrillation after cardiac surgery,[94 191] as well as after thoracotomy for lung resection.[100] Nonetheless, it was not until the late 1970s that it became generally accepted that patients taking β-AAs preoperatively should be continued on β-AA treatment perioperatively. In one study, Slogoff and colleagues[202] reported pre-bypass ischaemia in patients undergoing CABG surgery in 26% of patients with

Table 2 Classification of β-adrenergic antagonists

Generation, class	Characteristics	Examples
1st I	No ancillary properties	Propranolol, timolol, nadolol
2nd II	β_1-selective	Metoprolol, atenolol, bisoprolol, esmolol
3rd III	β_1-selective or non-selective, important ancillary properties	Carvedilol, celiprolol, bucindolol, nebivolol

propranolol treatment continued in full dosage until operation, in 50% of patients with propranolol withdrawal and in 70% of patients with no β-AA treatment.

Administration of perioperative β-AAs controls haemodynamic variables and successfully decreases the incidence of ischaemic events in patients with or at risk of coronary artery disease. This is particularly relevant as patients with perioperative ischaemia have a nine-fold increase in the risk of developing a serious adverse cardiac outcome during hospitalization and more than a two-fold increase in the risk of dying prematurely over the first 6 months after surgery.[140] Patients with a postoperative in-hospital myocardial infarction have a 28-fold increase in the rate of subsequent cardiac complications within 6 months, a 15-fold increase within 1 yr and a 14-fold increase within 2 yr. Stone and colleagues[212] administered a single oral preoperative dose of one of three different β-AAs (labetalol, oxprenolol, atenolol) to patients with mild uncontrolled hypertension undergoing non-cardiac surgery. The incidence of myocardial ischaemia was 28% in the untreated controls compared with 2% in the β-AA-treated patients, based on ECG criteria ($P<0.001$). Wallace and colleagues[231] administered i.v. atenolol preoperatively and i.v. and oral atenolol for up to 7 days postoperatively in patients with or at risk of coronary artery disease. Myocardial ischaemia was assessed by continuous three-lead Holter monitoring. Intraoperative myocardial ischaemia was reported to be 12% in each of the control and atenolol-treated groups. Conversely, the incidence of myocardial ischaemia was reported to be 34% in the control *vs* 17% in the treated patients in the first 48 h after surgery ($P<0.008$) and 39 *vs* 24% over days 0–7 ($P<0.029$). More recent studies by Raby and colleagues[179] and Urban and colleagues[225] confirm the powerful anti-ischaemic effect of perioperative β-adrenergic antagonism and re-emphasize the importance of stress-induced increases in heart rate in the pathogenesis of perioperative myocardial ischaemia. The association between the occurrence of perioperative myocardial ischaemic events, perioperative tachycardia and an adverse long-term cardiac outcome led to therapeutic trials with β-AAs. However, it should be noted at this point that the association between postoperative myocardial ischaemia and adverse cardiac events does not necessarily imply a causal relationship and that postoperative myocardial ischaemia may represent only a manifestation of the underlying cardiac disease. Factors other than reduced ischaemia may contribute significantly to the improvements in outcome observed after administration of β-AAs. These will be discussed extensively in this article. Using preoperative (1 h before surgery) and postoperative (until 7 days after surgery) atenolol (Table 1), Mangano and colleagues[142] demonstrated in a well-designed study a significant reduction in postoperative myocardial ischaemia in patients with or at risk of coronary artery disease. This reduction in ischaemic events was associated with a 55% decrease in overall mortality and a 65% decrease in cardiac mortality at 2 yr for the atenolol-treated patients. The protective effects of atenolol were evident in these patients 6 months after surgery (overall mortality 0 *vs* 8%, $P<0.001$) and were preserved over the 2-yr follow-up period (overall mortality 10 *vs* 21%, $P<0.019$). Recently, Poldermans and colleagues[173] randomized patients undergoing vascular surgery with mild to moderate positive stress echocardiography to preoperative (from 1 week before surgery) and postoperative (until 30 days after surgery) bisoprolol treatment or placebo (Table 1). After the inclusion of 112 patients, this study was halted for ethical reasons associated with large differences in morbidity and mortality rates between the placebo and bisoprolol arms of the study. Notably, the study reports a 10-fold decrease in the 30-day perioperative incidence of death from cardiac causes and non-fatal myocardial infarction in bisoprolol-treated patients (3.4 *vs* 34%, $P<0.001$). A critical evaluation of these studies has been published recently in the *British Journal of Anaesthesia* and can be recommended as additional reading.[96] Taken together, these data indicate that β-adrenergic antagonism remains the sole proven pharmacological means of reducing perioperative cardiovascular short- and long-term cardiac morbidity and mortality in patients with or at risk of coronary artery disease. In the light of the benefits of perioperative β-AAs and the exceptionally low complication rate associated with the perioperative use of β-AAs, future trials have to clarify whether the cumulative morbidity and mortality associated with sophisticated and expensive preoperative testing can be justified in high-risk cardiac patients undergoing surgery.[128 144 190]

New aspects of perioperative β-adrenergic antagonism have emerged recently. Johansen and colleagues[102 103] demonstrated that esmolol could potentiate the reduction in minimum alveolar concentration for isoflurane by alfentanil (–26%) and decrease anaesthetic requirements for skin incision during propofol/nitrous oxide/morphine anaesthesia (–27%) in patients. The clinical utility of this effect was subsequently demonstrated by Zaugg and colleagues[254] in a study with elderly surgical patients that evaluated three anaesthetic regimens, two of them with atenolol. High-dose intraoperative administration of atenolol decreased isoflurane requirements by 37% and still allowed an adequate depth of anaesthesia, as assessed by bispectral analysis (mean bispectral index $\approx$50–60). Pre- and postoperative atenolol as well as high-dose intraoperative atenolol also

Table 3 Ancillary properties of clinically used β-adrenergic antagonists. +=effect present, −=effect absent

Drug	β_1/β_2 selectivity	Membrane-stabilizing activity	Intrinsic sympathomimetic activity	Lipid solubility	Clearance	Special
Propranolol	2 1	+	−	+++	Hepatic	Inverse agonist
Metoprolol	74	−	−	+	Hepatic stereoselective	Inverse agonist
Atenolol	75	−	−	−	Renal	−
Esmolol	70	−	−	−	Erythrocytes	−
Bisoprolol	119	−	−	(+)	Hepatic/renal	−
Celiprolol	~300	−	+	−	Hepatic/renal	β_2-Agonist
Nebivolol	293	−	−	+	Hepatic	NO release, bronchodilation
Carvedilol	7.2	−	−	+	Hepatic stereoselective	Antioxidant, anti-adhesive, α_1-Antagonist
Bucindolol	1 4	−	+	+	Hepatic	α_1-Antagonist

decreased requirements for intraoperative fentanyl (–27%) and postoperative morphine (–40%). As a consequence, extubation time and recovery in the postanaesthesia care unit were significantly faster in patients treated with atenolol.

The present armamentarium of β-adrenergic antagonists

Although all β-AAs are able to antagonize the transduction of the β-adrenergic receptor signal (β-AR), this class of drugs is far from being homogeneous. Recently, antisense oligonucleotides against β_1-adrenergic receptor (β_1-AR) mRNA, which suppress protein translation at the ribosomes, have been constructed and used successfully to treat hypertensive rats.[258] Currently used β-AAs, however, competitively antagonize β-ARs and can be roughly classified into three generations depending on their ancillary properties (Table 2).[28 29] The main ancillary properties of individual agents include partial agonist activity (intrinsic sympathomimetic activity), β-receptor subtype specificity (β_1 *vs* β_2), lipophilicity and membrane-stabilizing activity (Table 3). Other ancillary properties include vasodilator effects [β_2 (celiprolol)-, anti-α_1 (carvedilol)- or nitric oxide (NO)-mediated effects (nipradilol, nebivolol)], class III anti-arrhythmic activity (sotalol), antioxidant effects (carvedilol) and stereoselective hepatic metabolism (carvedilol, metoprolol). Accordingly, carvedilol by oral administration exerts equal effects on α- and β-ARs, whereas carvedilol by i.v. administration exerts more β-AR effects than α-AR effects because of decreased stereoselective hepatic metabolism of the β-AR-specific *S*-isomer of carvedilol.[164] Interestingly, stereoselective metabolism of metoprolol may result in insufficient β-adrenergic antagonism in 'poor metabolizers' (*S*/*R* isomer ratio <1).[201 203]

Recent research in transgenic animal models also emphasizes the importance of the two-state model of β-AR activation in characterizing β-AAs (Fig. 1). This model proposes an equilibrium between an inactive and an active conformation of the receptor, which is differentially modulated by various ligands (concept of inverse agonism: neutral antagonist *vs* inverse agonist).[18] Notably, it predicts spontaneous activation of β-ARs, which was verified recently for the β_2- but not the β_1-AR.[261] This model also explains the inability of some β-AAs with pronounced neutral antagonism to block the effects of receptor overexpression fully, as neutral antagonists counteract activation by endogenous catecholamines but not activation by spontaneous transition into the active receptor conformation.[134] The physiological consequences are not yet determined fully but may be of clinical relevance with respect to the tolerability of various β-AAs and the treatment of the withdrawal syndrome. Finally, there is growing evidence that β-ARs differentially couple to various G-proteins depending on the specific properties of the ligand, thereby stimulating differential cellular responses.[233]

Interestingly, a meta-analysis of randomized controlled trials revealed differential effects on cardiovascular events, such as reinfarction and sudden cardiac death, metoprolol being more effective than atenolol or propranolol. This led the authors to conclude that the so-called class effect of β-AAs may be less important than ancillary properties.[204] However, the mechanistic concept of the class effect is greatly supported by the observation that selective as well as non-selective β-AAs decrease mortality significantly in chronic heart failure.[121] Nonetheless, ancillary properties are important with respect to the side-effects and tolerability of the specific agents, which will be discussed separately.

Mechanisms and sites of action

The following sections will focus on the mechanisms and sites of action elicited by β-AAs.

Cardiac considerations

Bradycardia, the link to many cardioprotective effects of β-adrenergic antagonists

Elevated heart rate is a well-established independent predictor of coronary artery disease and cardiovascular morbidity and mortality.[168] Also, delayed decrease in heart

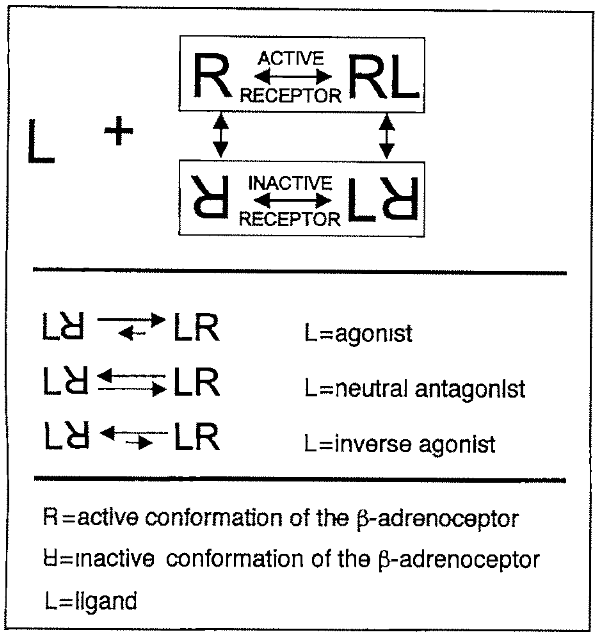

Fig 1 Two-state model of β-adrenergic receptor activation by competitive ligands Signalling at the receptor includes binding of the ligand to the extracellular binding domain, transduction of the signal through conformational changes of the receptor and activation of the effector (G-protein complex) In the absence of a ligand, the receptor can undergo spontaneous transition from the inactivated to the activated state Ligands can be classified into agonists, neutral antagonists and inverse agonists according to their tendency to shift this equilibrium The agonist shifts the equilibrium towards the active state and the inverse agonist shifts it to the inactive state Although most β-adrenergic antagonists (β-AAs) act as inverse agonists, some β-AAs with weak inverse agonism may be classified as neutral antagonists [18] The relative degree of inverse agonism increases in the following order bucindolol<carvedilol <propranolol<metoprolol [249] This model explains the observed lower tolerability of patients treated with inverse β-AAs: they shift the receptor population almost completely to the inactive state, particularly when the sympathetic basal tone is low On the other hand, β-AAs with weak inverse agonism leave a sizeable fraction of the receptor in the active state, thus explaining their better tolerability in clinical use

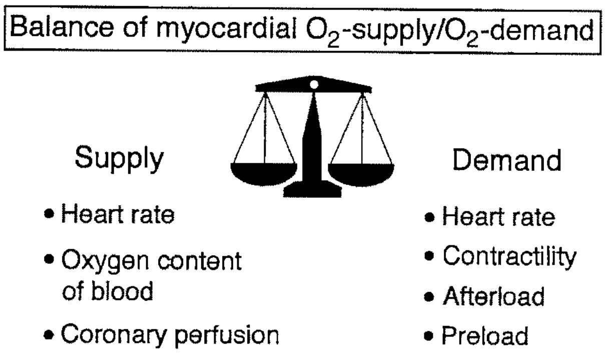

Fig 2 Myocardial oxygen balance In patients with coronary artery disease, tachycardia decreases myocardial oxygen supply and concomitantly increases oxygen demand

rate after graded exercise predicts cardiovascular mortality.[38] Bradycardia is suggested to be one important mechanism of cardioprotection elicited by β-AAs. Importantly, a negative chronotropic response to β-AAs is preserved among diabetic patients with progressive autonomic dysfunction.[111]

In the perioperative period, increased heart rate is strongly associated with myocardial ischaemia.[141] [143] Accordingly, myocardial oxygen balance is closely related to heart rate and must be examined on a beat-to-beat basis (Fig. 2). Increased heart rate results in elevated myocardial oxygen demand via the Bowditch effect, which is, however, nearly offset by decreased oxygen demand caused by the lower ventricular wall tension at higher heart rates. Because increased heart rate is usually accompanied by increased inotropy and the length of diastole is significantly decreased in tachycardia, myocardial oxygen balance can deteriorate seriously at higher heart rates in patients with coronary artery disease. Increased left ventricular stiffness further exacerbates impairment of ventricular filling. Importantly, the heart rate at which patients are considered at risk of developing ischaemia is not absolute and must be individualized. Patients with severe angiographic narrowing of the coronary arteries show a gradual decrease in cross-sectional area by 32% when heart rate reaches 90 beats min^{-1}.[160] Therefore, it is not surprising that patients with coronary artery disease and a heart rate greater than 100 beats min^{-1} almost inevitably develop myocardial ischaemia.[69]

The deleterious effects of an increased heart rate on infarction size have been reported Augmentation of heart rate after experimental coronary occlusion in dogs, by ventricular pacing, isoproterenol or atropine, leads to increases of 40, 70, and 40% respectively in myocardial necrosis when compared with control.[199] Consistent with this notion, thiopental given during coronary occlusion doubles infarction size by increasing heart rate. Notably, tachycardia also accentuates endomyocardial to epimyocardial maldistribution of ventricular blood flow in ischaemia.[12] β-AAs effectively reverse all these untoward effects by lowering heart rate.[227] β-AAs also exert a beneficial effect in coronary artery disease by decreasing the stiffness of atherosclerotic plaques, which results in increased tensile strength.[127] The stiffness of fibrous caps of human atherosclerotic plaques is directly related to heart rate, and increased heart rate promotes the fissuring of atherosclerotic plaques. β-AAs prevent the rupture of vulnerable atherosclerotic plaques, which leads to less inflammation in the plaque and decreases the gradual narrowing of the vessel lumen.[63] [66] [178] Furthermore, tachycardia causes activation of platelets.[54] When coronary blood flow increases, platelets can be traumatized and activated across the coronary bed, particularly at sites with significant narrowing. Histopathological analyses of perioperative myocardial infarction stress the importance of plaque disruption and thrombosis as pivotal steps in the pathogenesis of perioperative myocardial infarction.[48] Alternatively, long-duration subendocardial ischaemia and subsequent non-Q-wave infarction resulting from prolonged tachycardia were also proposed as the underlying mechanism of perioperative myocardial infarction.[124] The view that postoperative myocardial ischaemia is a mere manifestation of the underlying cardiac disease is specifically supported by the findings of the post-mortem study by Dawood and colleagues.[48] In this study, fatal postoperative myocardial infarctions were associated with evidence of unstable plaques in 55% of the patients. In contrast, imbalance of myocardial oxygen supply/demand may play a causal role in the pathogenesis of postoperative cardiac events. This view is supported by the fact that most postoperative myocardial infarctions are non-Q-wave infarctions that are preceded by long-duration (>2 h) postoperative ischaemia.[125] Because cardiac complications are preceded by long-duration ST-segment depression rather than elevation, it seems plausible that the cascade of events leading to postoperative cardiac complications does not begin with acute coronary occlusion but with long-duration subendocardial ischaemia. This is further supported by a recent study by Badner and colleagues,[8] which determined the incidence of postoperative myocardial infarction after non-cardiac surgery in a large group of patients at high risk. This study also reports the preponderance of non-Q-wave infarction, which differs from that seen in non-surgical patients presenting to the emergency room. From a mechanistic point of view, non-Q-wave infarctions result from prolonged ischaemia rather than from total occlusion of the coronary arteries. Certainly, further studies are needed to elucidate the role of postoperative myocardial ischaemia in the cascade of events leading to perioperative cardiac morbidity and mortality.

The institution of bradycardia was recently found to cause restoration of contractile function in a canine model of mitral regurgitation-induced left ventricular dysfunction.[161] In this model, optimized myocardial Ca^{2+} handling and bioenergetics are direct consequences of bradycardia and are suggested to be responsible for the observed improvement in contractility.[257]

At the cellular level, rapid electrical stimulation of contraction reduces the density of β-ARs and their responsiveness,[116] which appears to be associated with disassembly of microtubules secondary to undue micromechanical stress.[248]

Cardioprotective effects of β-adrenergic antagonists not apparently associated with bradycardia

Stangeland and colleagues[207] addressed the important question of whether decreased heart rate is the only mechanism responsible for cardioprotection elicited by β-AAs. They treated anaesthetized cats with alinidine (a clonidine analogue that decreases heart rate independently of β-ARs) or timolol. Heart rate was similarly reduced by 40 beats min^{-1} in the treatment groups compared with the control group, and regional ischaemia was induced by occluding the left descending coronary artery. After 6 h of ischaemia, the necrotic tissue was measured and expressed as a percentage of necrotic tissue in the area at risk. Notably, alinidine significantly decreased necrosis from 87% present in the control group to 77% (P<0.01), whereas timolol decreased necrosis to 65% (P<0.001). This observation clearly indicates that mechanisms other than decreased heart rate contribute substantially to cardioprotection by β-AAs.

β-Adrenergic signal transduction in cardiomyocytes. Biological responses mediated by β-ARs involve positive chronotropy, dromotropy, inotropy and cardiomyocyte growth and death (Fig. 3). β-ARs are members of the G-protein-coupled superfamily, which share the characteristic feature of the seven-transmembrane-spanning domains. In healthy mammalian cardiomyocytes, β_1-ARs constitute around 70–80% of the β-ARs in human and rat hearts.[52 236] In many disease states with heightened sympathetic drive, β_1-ARs are down-regulated by phosphorylation (desensitization), translocation (sequestration) and finally by degradation of the receptor.[88] Conversely, β_2-ARs do not decrease in number; however, they show some loss of contractile response to agonist stimulation as a result of the up-regulation of β-AR kinases (β-ARK) and Gi proteins (Table 4).[26] In the failing human heart, β_2-ARs represent 40% of β-ARs and are of great importance in mediating inotropic and chronotropic responses.[25] Key steps in signal transduction of β_1- and β_2-ARs involve coupling to G-proteins and activation of the cAMP/protein kinase A (PKA) pathway, which leads to phosphorylation of target proteins such as phospholamban, the ryanodine receptor, troponin I and L-type Ca^{2+} channels.[209 244] However, apart from changes in myocardial contractile function, β-ARs exert important effects on cellular metabolism, growth and death (gene expression) through the activation of PKA and protein kinase C (PKC).[90] Because the β_1-AR and the β_2-AR share only 54% of amino acid sequences overall, it is possible that β-AR subtypes couple to distinct signal transduction pathways.[243 245] Although both β_1- and β_2-ARs increase the contractile response and hasten relaxation in ventricular myocytes, several striking differences with respect to G-protein binding characteristics and signal transduction downstream from the receptor have been revealed. In contrast to β_1-ARs, β_2-ARs exhibit dual coupling to Gs and Gi that can completely negate Gs-mediated responses. Also characteristic of β_2-mediated signalling is the exceptionally modest increase in cAMP and the compartmentalized increase in PKA activity, which is restricted to the vicinity of L-type Ca^{2+} channels.[124 260] Finally, β_2-ARs may also bind to Gq-activating phospholipase C (Fig. 3). These data indicate that β-AR subtypes differentially modulate cardiac function and cardiomyocyte phenotype. Therefore, the subtype specificity of various β-AAs affects biological responses significantly.

Little is known about the role of β_3-ARs in cardiomyocytes. Whereas β_3-ARs are known to exert important physiological effects in brown adipose tissue, gut relaxation and vasodilation, β_3-ARs mediate negative inotropy by a NO-dependent pathway in cardiomyocytes.[70 226] Studies

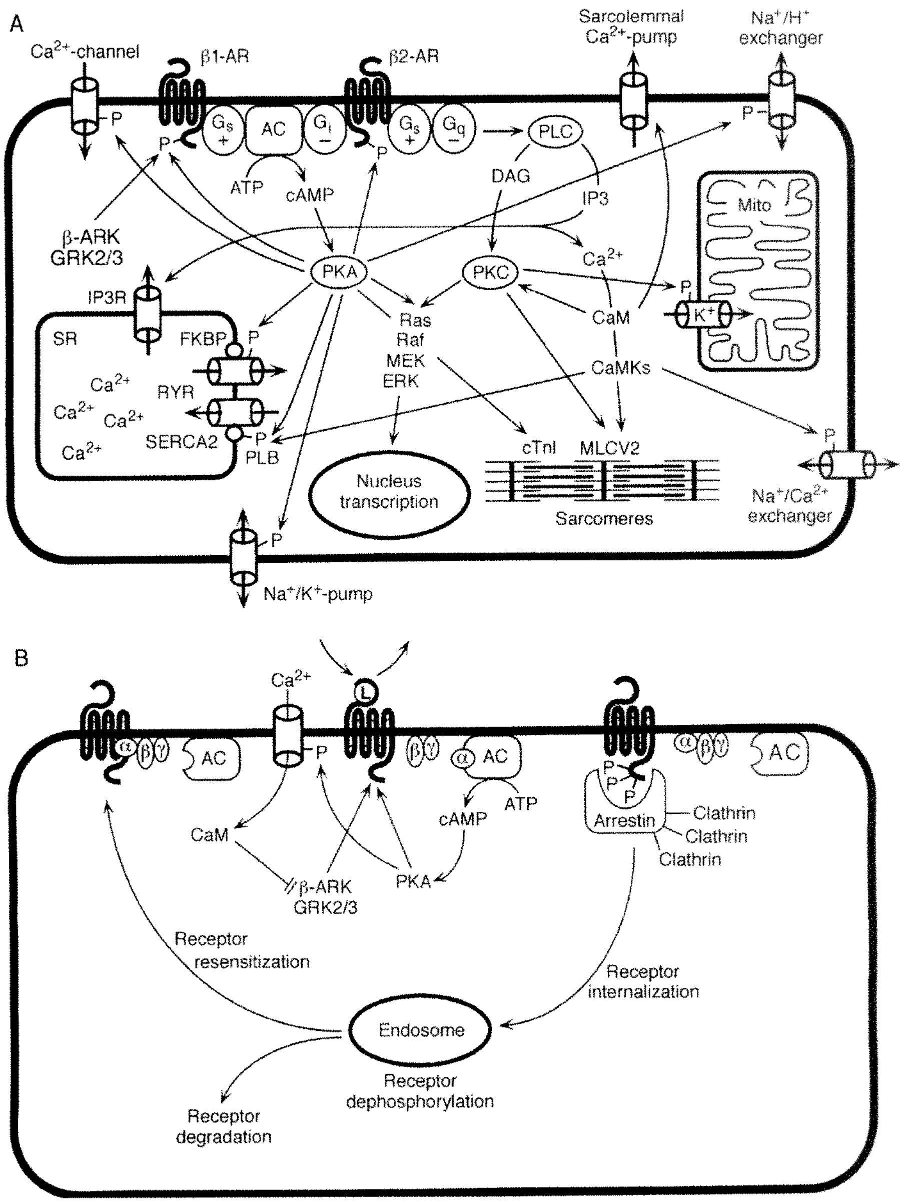

Fig 3 β-Adrenergic signalling cascades in cardiomyocytes. (A) Binding of an agonist (L) to either the β_1- or the β_2-adrenergic receptor (β_1-AR, β_2-AR) stimulates Gs protein, which dissociates from the receptor and binds to adenylate cyclase (AC), causing production of cAMP from ATP and activation of protein kinase A (PKA). G-protein-coupled receptors interact by their intracellular loop 3 with the heterotrimeric G complex and promote GDP release. PKA phosphorylates the voltage-dependent L-type Ca^{2+} channels, the Na^+/H^+ exchange channels and the Na^+/K^+ pump at the sarcolemma, phospholamban (PLB) and the ryanodine receptor (RYR) at the sarcoplasmic reticulum (SR) and cardiac troponin-I (cTnI) in the sarcomeres, leading to increased inotropic and lusitropic (relaxation) responses. In contrast, the β_2-AR is also able to couple to Gi or Gq proteins. Gi inhibits adenylate cyclase (AC) and opposes the effects of Gs. Gq activates phospholipase C (PLC). By splitting phosphatidylinositol bisphosphate, PLC liberates the two intracellular second messengers diacylglycerol (DAG) and inositol trisphosphate (IP3). IP3 binds to the IP3 receptor (IP3R), which releases Ca^{2+} from the SR. Ca^{2+} combines with calmodulin (CaM) and directly activates the sarcolemmal Ca^{2+} pump as well as several CaM-dependent protein kinases (CaMKs). This signalling pathway leads to phosphorylation of PLB, ventricular myosin light chain 2 (MLCV2) and the Na^+/Ca^{2+} exchanger. DAG and CaM together activate PKC, which in turn phosphorylates the mitochondrial ATP-dependent K^+-channel and MLCV2. In its unphosphorylated state, the regulatory protein PLB is bound to the SR Ca^{2+}-pump (SERCA2), inhibiting its activity. When phosphorylated by PKA and/or CaMK, it dissociates from SERCA2, relieving the inhibitory effect. On the other hand, direct phosphorylation of RYR at Ser-2809 dissociates the regulatory component FKBP (FK506 binding protein), leading to increased activity of the RYR channel. PKA and PKC both affect gene expression in the cell nucleus via the common MAPK (mitogen-activated protein kinases) signalling pathway: Ras (monomeric GTPase), Raf (a MAPKKK), MEK (mitogen-activated ERK activating kinase) and ERK (extracellular signal regulated kinase). To protect the cardiomyocyte from β-adrenergic overstimulation, a negative feed-back loop (not shown in the diagram) is built in, which degrades cAMP to AMP by means of CaM-activated phosphodiesterase III. (B) Diagram showing in more detail the dissociation of the heterotrimeric G complex from the β-AR upon binding of the agonist (L). After this dissociation, the adenylate cyclase (AC) becomes activated by binding to the α-subunit. Desensitization of the β_1- and β_2-ARs is mediated by phosphorylation of the intracellular C-terminal part of the receptor by either PKA or the β-adrenergic receptor kinase (β-ARK, GRK2 and 3). Binding of arrestin and clathrin to the phosphorylated β-AR mediates internalization to the endosome. After dephosphorylation, β-ARs may be either degraded or resensitized. Note that an additional negative feed-back loop leads to inhibition of the β-ARK via increased Ca^{2+}-calmodulin (CaM).[17 58 90 147 148 171 189]

Table 4 Major changes in components of β-adrenergic signalling in the failing human heart[28 147 171]

	mRNA	Protein	Function
Signalling components			
β_1-ARs	↓	↓	↓
β_2-ARs	←→	←→	←→
Gs protein	←→	←→	←→
Gi protein	↑	↑	↑
β-adrenergic receptor kinase (β-ARK)	↑	↑	↑
Adenylate cyclase	↑	?	↓
Intracellular Ca^{2+} handling			
L-type Ca^{2+} channel	←→	←→	←→
Na$^+$/Ca^{2+} exchanger	↑	↑	↑
SR Ca^{2+} pump (SERCA2)	↓	↓	↓
Phospholamban	←→	←→	↑

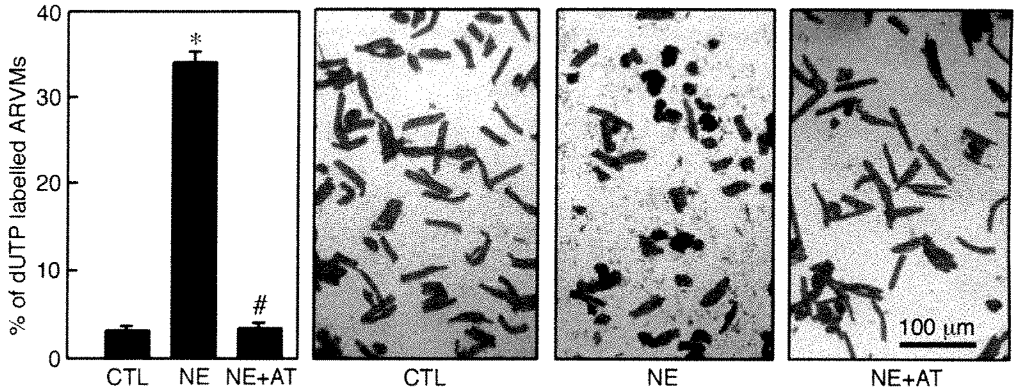

Fig 4 Cardiotoxicity of catecholamines. Adult rat ventricular myocytes (ARVMs) grown on coverslips were exposed to norepinephrine (NE) (10 μmol litre^{-1}) alone or in the presence of atenolol (AT) (10 μmol litre^{-1}) for 12 h and subjected to TUNEL (terminal dUTP nick end labelling) staining, which is specific for apoptotic cell death. (A) Mean percentage of TUNEL-positive ARVMs on coverslips. Data are mean (SEM). $^*P<0.0001$ *vs* control; $P<0.0001$ *vs* NE. (B) Control ARVMs with rod-shaped morphology. (C) NE-exposed ARVMs with rounded morphology and black apoptotic nuclei. (D) NE+AT-treated ARVMs. Note preservation of rod-shaped morphology with NE treatment (reproduced with permission from *Circulation*[255]).

evaluating the distribution and quantification of β_1/β_2/β_3-AR subtypes in heart tissue have revealed subtype proportions for the left porcine ventricle as follows: β_1:β_2:β_3=72%:28%:0.25%.[151] This implies that, in the normal myocardium, β_3-AR may be of less importance. However, recent observations in heart failure patients demonstrate that opposite changes in the abundance of β_1-AR (down-regulation) and β_3-AR (up-regulation) occur and may play a role in the progressive functional degradation in the failing human heart.[155]

Cell death signalling: apoptosis and necrosis. Catecholamines, although beneficial in the short-term cardiovascular response, exert significant cardiac toxicity. The toxic effects of catecholamines on cardiomyocytes have been known since the beginning of the 20th century.[82] However, necrotic and apoptotic cell death has been closely related to enhanced β-adrenergic signalling only recently.[145] Apoptotic cardiomyocyte death by activation of the β-adrenergic signalling pathway was reported in norepinephrine-stimulated adult rat ventricular myocytes.[39] Zaugg and colleagues[255] further demonstrated that apoptotic cardiomyocyte cell death is dissociated from β_2-ARs and selectively mediated by β_1-ARs in adult ventricular myocytes (Fig. 4). This is in line with clinical observations that cardiac lesions associated with massive catecholamine bursts were prevented with atenolol in patients with subarachnoid haemorrhage.[43] Communal and colleagues[40] and Chesley and colleagues[36] further showed that β_2-AR stimulation may protect cardiomyocytes from apoptosis-inducing stimuli. The abilities of β-AR stimulation and tachycardia to induce cardiomyocyte apoptosis were addressed by Shizukuda and colleagues[200] in an *in vivo* rat model. Rats were treated with placebo or isoproterenol to establish whether catecholamines *per se* in the absence of significant increases in systolic load and tachycardia induce myocardial damage via apoptosis. After only 24 h of isoproterenol treatment, a significant increase in apoptotic events was detected. Animals exposed to ventricular pacing to induce tachycardia equivalent to that produced by isoproterenol treatment did not show an increase in

Table 5 Gene-targeted mice mimicking enhanced β-adrenergic signalling

Cardiac-specific overexpression of (increase in expression compared with control)	**Changes in phenotype/outcome**
Gsα (×3–5)[71]	Hypertrophy, apoptosis, premature death due to congestive heart failure
Gqα (×2–4)[45]	Hypertrophy, apoptosis, premature death due to congestive heart failure
β_1-AR (×5)[61]	Hypertrophy, apoptosis, premature death due to congestive heart failure
β_2-AR (×30–60)[134]	Enhanced cardiac function, no long-term adverse effects
β_2-AR (×200)[42, 56]	Enhanced cardiac function, but long-term adverse effects decrease recovery after ischaemia and premature death with aortic constriction
β_2-AR (×350)[134]	Hypertrophy, apoptosis, premature death due to congestive heart failure
Gqα+β_2-AR (×30)[55]	Reversal of hypertrophy and prevention of death from cardiac cause induced by Gq overexpression

apoptosis. The authors concluded that apoptotic cardiomyocyte death resulting from isoproterenol treatment may not be explained by increased heart rate alone. Conversely, in a canine model, rapid ventricular pacing *per se* increased apoptotic cell death and led to cardiac myopathy.[136] Importantly, decreased apoptosis has been reported in carvedilol- and propranolol-pretreated rabbit hearts subjected to ischaemia–reperfusion injury.[252] Because apoptotic cell death occurs in only a few hours, apoptosis may be an important mechanism for loss of viable cardiomyocytes and myocardial dysfunction in the immediate perioperative period.[253]

New insight from gene-targeted animals. While experimental results indicate incontrovertibly that enhanced β_1-AR signalling is exceptionally cardiotoxic, data on the effects of the β_2-AR with respect to beneficial and detrimental effects are contradictory. Recent research in the field of heart failure tried to construct genetically altered mouse models mimicking increased sympathetic nervous system activity (Table 5). In particular, transgenic mouse models with cardiac-specific overexpression of various G-proteins and β-AR subtypes were constructed.[3, 45, 61, 71, 134, 153] Mice with Gsα overexpression typically develop a characteristic hypertrophic cardiomyopathy at 15 months of age. Sections of these hearts reveal hypertrophic myocytes with increased cross-sectional areas and an increased number of apoptotic myocytes. Importantly, propranolol, a non-selective β-AA, abolished the hypertrophic response and the development of dilated chambers, thereby improving survival. Similar results were reported for mice overexpressing Gqα- and β_1-AR. Notably, mice with only five-fold overexpression of the β_1-AR develop fatal cardiomyopathy,[61] whereas mice with 30- to 60-fold overexpression of the β_2-AR exhibit enhanced cardiac function and do not develop overt cardiomyopathy.[134] Although no long-term toxic effects were reported by some authors in mice with 200-fold overexpression of the β_2-AR,[209, 244] increased susceptibility to ischaemic injury[42] and augmented afterload[56] were clearly observed. Nonetheless, it was suggested that manoeuvres that serve to augment β_2-adrenergic signalling, which improves systolic and diastolic function, may offer a potential therapeutic approach in patients suffering from impaired cardiac function. For this purpose, pharmacological means and ultimately *in vivo* gene transfer strategies were proposed and investigated.[110, 150, 196] Accordingly, the contractility of single myocytes isolated from the ventricles of rabbits chronically paced to produce heart failure can be functionally restored by adenovirus-mediated transfer of β_2-ARs.[4] Consistent with this notion, a dual-expressing ‘designer’ mouse with cardiac-specific Gqα expression and concomitant β_2-AR expression at low (30×), medium (150×) and high levels (1000×) was constructed recently.[55] Gqα mice with low concomitant expression of β_2-ARs, i.e. a ~30-fold increase in β_2-AR compared with wild type, displayed rescue of hypertrophy and ventricular function. Importantly, these effects occurred in the absence of any improvement in basal or agonist-stimulated adenylate cyclase (AC) activity, indicating the restoration of a compartmentalized β_2-AR–AC signalling pathway.[124, 260] The summarized experimental results, which clearly demonstrate beneficial effects of modest β_2-adrenergic signalling in an animal model of heart failure, have found their clinical counterpart very recently.[30] Studies of β_2-AR gene variations in twins revealed that specific β_2-AR polymorphisms, which resulted in enhanced down-regulation of the β_2-AR, increased cardiac dimensions (septum thickness, posterior wall thickness, left ventricular mass).

In summary, the concept that β-adrenergic signalling may not mediate deleterious effects exclusively but may also have beneficial effects in the compromised heart is based on several experimental observations. In this regard it is interesting to note that, in patients with symptomatic heart failure, pan-adrenergic antagonism using central sympatholysis (moxonidine, an α_2-agonist) was terminated because of excess mortality.[121] β_2-AR agonism as an adjunct to β_1-AR antagonism may therefore have the potential to improve the therapeutic tolerance, particularly during the initiation of β-AA therapy, and to improve survival in the treatment of the failing heart. Interestingly, β_1-AR antagonism enhances the β_2-AR-mediated inotropic response to catecholamines, which may, in part, also explain the better tolerability of selective β_1-AAs.[84]

Mechanical unloading and modulation of gene expression. β-AAs allow the heart to ‘rest’ by emulating a state of ventricular unloading. Accordingly, the expression of tumour necrosis factor α (TNF-α), an indicator of increased mechanical load, is similarly reduced by β-AAs and by mechanical circulatory support.[174 221] High-dose atenolol also prevents angiotensin II- and tachycardia-induced activation of metalloproteinases and diastolic stiffening.[195] Changes in gene expression caused by β-AAs also involve a decrease in endothelin-1[68] and sarcoplasmic reticulum proteins[217] and an increase in atrial natriuretic factor.[250] Furthermore, carvedilol decreases Fas receptor expression (cell death signalling receptor) after ischaemia–reperfusion injury, which leads to decreased apoptotic cell death.[252] Taken together, these observations suggest altered gene expression as a potential site of cardioprotection by β-AAs.

Platelet aggregability and coagulation. The adrenergic system influences coagulation and fibrinolysis, particularly during episodes of heightened adrenergic drive, but contributes much less to baseline levels of coagulatory and fibrinolytic function. Epidemiological studies revealed a significant morning increase in the incidences of infarction, sudden cardiac death and transient myocardial ischaemia, which appears to be related to increased morning catecholamine levels and coagulation.[158 238] Perioperatively, increased catecholamine levels and tissue damage greatly increase the propensity to coagulation. Propranolol decreases thromboxane synthesis and platelet aggregation in patients receiving long-term propranolol treatment.[32] One study evaluating the effect of metoprolol on platelet function did not find any inhibitory effect,[239] whereas another study reports decreased platelet aggregability in patients with stable angina being tested for exercise stress.[241] Metoprolol also prevents stress-induced endothelial injury by increasing prostacyclin biosynthesis[75] and decreasing epinephrine-induced increases in von Willebrand factor antigen.[126] Esmolol has *in vivo* inhibitory action on neutrophil superoxide generation and platelet aggregation in a canine model of myocardial ischaemia—reperfusion.[186] β-AAs also decrease the affinity of low-density lipoprotein to arterial proteoglycans and endothelial wall damage by reducing plasminogen activator inhibitor-1.[216] Conversely, increased platelet aggregability and decreased platelet cAMP production were reported after timolol treatment.[240]

β-Adrenergic receptor down-regulation and target protein hyperphosphorylation. Prolonged and intensive perioperative agonist stimulation leads to desensitization and down-regulation of β-ARs, which may seriously impair cardiac function.[28 29] Conversely, down-regulation of the sensitivity and number of receptors may be beneficial with respect to arrhythmogenicity.[251] Tachycardia,[116] free oxygen radicals[133] and increased serum levels of TNF-α,[79] which are, notably, all factors significantly affected by β-AAs, were further implicated in the down-regulation of β-ARs and the subsequent attenuated cardiovascular response. Importantly, down-regulation occurs after only a few hours of agonist stimulation.[88] At the molecular level, the process involves uncoupling of the β-AR from Gs-proteins by PKA and β-adrenergic receptor kinase 1 (β-ARK) and binding of inhibiting arrestin to the receptor, which is followed by internalization and degradation or resensitization of the receptor (Fig. 3B). Early uncoupling and late down-regulation of myocardial β-ARs were reported after cardiopulmonary bypass.[72 193] Similarly, persistent down-regulation and desensitization of β-ARs were reported after thoracotomy or laparotomy throughout the first week after surgery.[5] Hyperphosphorylation of channels and regulatory proteins such as the sarcoplasmic ryanodine receptor (RYR) may occur, resulting in hypersensitivity to cytosolic Ca^{2+}.[147 148] β-AAs potentially prevent hyperphosphorylation in the perioperative period, which is similar to their effects in congestive heart failure.[91]

Anti-arrhythmic effects. Sustained arrhythmias may be haemodynamically relevant and may affect the outcome adversely.[13] Almost half of all high-risk cardiac patients undergoing non-cardiac surgery have ventricular ectopic beats or some sort of ventricular tachycardia.[166] Patients undergoing cardiac surgery have a high risk of developing new-onset atrial fibrillation.[6] From a mechanistic point of view, sympathetic tone plays an important role in most ventricular as well as atrial arrhythmias.[192] β-AAs shift the autonomic balance towards a higher vagal and lower sympathetic tone.[224] Studies on infarctions in pigs clearly showed that β-adrenergic mechanisms play a major role in ventricular fibrillation threshold during experimental coronary occlusion.[119] This is consistent with the notion that β-AAs prevent sudden electrical cardiac death.[62 112] Regarding atrial arrhythmias, β-AAs may be superior to newer class-III anti-arrhythmic drugs in the treatment of perioperative atrial fibrillation, as these drugs carry the risk of drug-induced polymorphic ventricular tachycardia. Notably, β-AAs also counteract epinephrine-induced hypokalaemia, which significantly predisposes to arrhythmias.

Bioenergetics. β-AAs are known to reduce NADH oxidase activity in mitochondria, which may lead to an energy-sparing effect.[177] Also, β-AAs shift cellular metabolism from fatty acid oxidation to glucose utilization, which effectively reduces the myocardial oxygen requirement.[22] Recently, oxidative metabolism was evaluated in patients with ventricular dysfunction using C-11-acetate positron emission tomography. The results of this study showed a significant reduction in cellular oxidative metabolism under metoprolol treatment.[10] Accordingly, in patients undergoing cardiopulmonary bypass, chronic propranolol treatment reduces oxygen consumption.[108] Interestingly, patients receiving chronic β-AA treatment compensate for reduced arterial oxygen content by increases in cardiac output and oxygen extraction, whereas patients not receiving β-AA treatment demonstrate only an increase in oxygen extraction.[206] Reduced production of lactate during exercise and increased oxygen extraction as a result of decreased cardiac output were reported previously under β-adrenergic antagonism.[175] β-AAs also prevent the decrease in mitochondrial CK activity after myocardial infarction.[97]

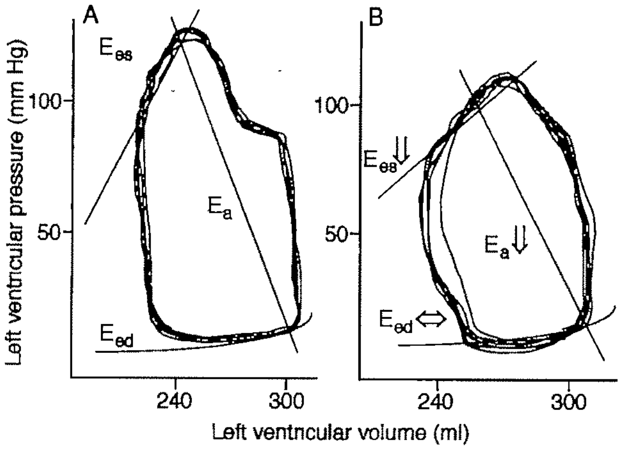

Fig 5 Schematic depiction of left ventricular volume–pressure loops in a patient with heart failure. (A) Volume–pressure loop without β_1-adrenergic receptor (AR) antagonism (B) Volume–pressure loop with acute exposure to β_1-A antagonism End-systolic elastance (E_{es}) is decreased under β_1-AR antagonism, which is accompanied by decreased cardiac output, decreased stroke volume and decreased +dP/dt$_{max}$. In contrast, whereas the duration of active isovolumetric relaxation may increase only slightly (decrease in –dP/dt$_{max}$), passive diastolic function, as indicated by end-diastolic elastance (E_{ed}, chamber stiffness), remains largely unaffected by β_1-AR antagonism. Importantly, afterload, as indicated by arterial elastance (E_a), is decreased by β_1-AR antagonism. Also, the ratio E_{es}/E_a, which represents ventriculoarterial coupling (the relationship between systolic function and afterload), is well preserved. Note that the area enclosed by the volume–pressure loops is closely related to myocardial oxygen consumption and is markedly reduced by β-AAs.

Neuroendocrine stress response. There is a reduction in renin activity by selective as well as non-selective β-AAs mediated by antagonizing β-ARs, and some studies have even reported decreased catecholamine release after initiation of β-adrenergic antagonism.[157] Most studies, however, did not observe a decrease in catecholamine serum levels[254] but rather an increase.[93] One study in pigs reported decreased neuropeptide Y serum levels associated with increased heart rate variability after treatment with metoprolol.[1]

Preconditioning. Theoretically, β-AAs may prevent preconditioning of the heart, which renders it more resistant to subsequent sustained ischaemia. However, metoprolol does not neutralize the favourable effects of preconditioning.[237] On the contrary, nipradilol, a nitric oxide-generating β-AA, clearly induces preconditioning by itself.[95]

Non-cardiac considerations

Effects of β-adrenergic antagonism on core components of an anaesthetic regimen

Anaesthetic and analgesic requirements. Previous studies focused on the anti-ischaemic properties of peri- and intraoperative β-adrenergic antagonism. Recently, it was shown that esmolol can potentiate the reduction in the minimum alveolar concentration (MAC) for isoflurane (–26% at esmolol 250 $\mu g\ kg^{-1}\ min^{-1}$) and decrease anaesthetic requirements for skin incision during propofol/nitrous oxide/morphine anaesthesia (–27% at esmolol 250 $\mu g\ kg^{-1}\ min^{-1}$).[102 103] Esmolol also decreases nociception in a variety of experimental settings, suggesting the potential to decrease the intraoperative anaesthetic requirements.[47] Altered distribution and decreased metabolism of opioids by β-AAs may underlie this anaesthetic-sparing effect.[182] Furthermore, although β-AAs *per se* do not provide analgesia or hypnosis, they are known to have central nervous system modulating activities and anxiolytic effects.[76 146 158] β-AAs potentially affect central nervous system pathways, which include neurones in the hypothalamus, hippocampus and cerebral cortex.[120 234] Accordingly, the favourable changes in heart rate variability after β-AA treatment are ascribed to lower activity of the central sympathetic nervous system. In mice and rats, the locus coeruleus-associated noradrenergic system participates in arousal, and β-adrenergic antagonism within this region reduces forebrain electroencephalographic activity.[16] Similarly, amphetamine-induced activation of the rat forebrain is clearly inhibited by timolol, and in humans norepinephrine is known to enhance the responsiveness of the cerebral cortex to excitatory neuronal transmission.[15 181] Notably, pure β-adrenergic antagonism is crucial for the observed anaesthetic-sparing effect because labetalol increases the anaesthetic requirement.[47] Even though esmolol and atenolol are hydrophilic β-AAs, they produce the same plasma/cerebrospinal fluid ratio as lipophilic β-AAs, thereby affecting the centrally located surface β-ARs.[120] Another mechanism that may significantly contribute to the anaesthetic-sparing effect elicited by β-AAs involves decreased excitatory stimulation of central nervous effector sites of hypnosis and somatic response. In this case, peripheral interruption of centripetal β-adrenergic autonomic pathways, like spinal and epidural anaesthesia, decreases afferent input and anaesthetic requirement.[163]

Memory storage. β-AAs also possess attenuating effects on memory storage. Effects of opioids on memory are known to be mediated through noradrenergic influences.[98] Importantly, propranolol was reported to impair memory storage of particularly emotional events in humans.[31] Also, β-AAs impair arousal-induced enhancement of working memory in elderly patients.[165] As intraoperative recall and subconscious processing of information is particularly increased for emotionally charged information,[132] it is tempting to speculate that β-AAs, as anaesthetic adjuvants, might actually decrease the risk of intraoperative awareness and recall. However, this may be different for haemodynamically compromised patients with concomitant cardiovascular medication. Nonetheless, adequate depth of anaesthesia, as indicated by the bispectral index, was achieved in a group of elderly patients using high-dose intraoperative atenolol and a restricted amount of anaesthetic.[254]

Table 6 Haemodynamic effects of β-adrenergic antagonists (β-AA), phosphodiesterase 3 inhibitors (PDE3I) and their combination in heart failure patients

Variable	**β-AA**	**PDE3I**	**β-AA+ PDE3I**
Heart rate	↓	↑	↓
Systolic function	↓ then ↑	↑	↑
Diastolic function	⟷ or ↑	↑	↑
End-diastolic pressure	⟷ then ↓	↓	↓
Myocardial oxygen consumption	↓	⟷ or ↑	↓
Propensity to arrhythmia	↓	↑	⟷

Recovery. Faster recovery from anaesthesia was reported in patients receiving propranolol or metoprolol[101,208] and in patients receiving intra- or perioperative atenolol.[254] Titration of anaesthetics to heart rate and blood pressure without administration of β-AAs may lead to prolonged recovery from anaesthesia as a result of 'relative overdosing' with administered anaesthetics ($\text{MAC}_{\text{BAR}} > \text{MAC}_{\text{AWAKE}}$).[183] Furthermore, specific properties of β-AAs may alleviate recovery from anaesthesia. In cats receiving atenolol, waking times were significantly prolonged,[92] and human sleep disturbance is a well-known side-effect of β-AAs.[159]

Immune response and β-adrenergic antagonism
The perioperative stress response impairs immune competence, particularly natural killer cell cytotoxic activity.[220] In the experimental setting, reduction of natural killer cell cytotoxicity was achieved by electrical stimulation of the splanchnic nerve in rats, and was completely antagonized by nadolol.[109] Recently, Ben-Eliyahu and colleagues[14] reported that hypothermia in barbiturate-anaesthetized rats suppresses natural killer cell cytotoxic activity and thereby accelerates the spread of tumour cells. Interestingly, nadolol attenuated the effect of hypothermia on natural killer cells and increased resistance to tumour metastasis.

Tolerability of perioperative administration of β-adrenergic antagonists

Contraindications to the use of β-AAs result directly from their anti-adrenergic action. Drug intolerance greater than 20% as a result of decreased contractile function and increased afterload were previously reported in first-generation compounds.[215] However, drug tolerability for second-generation compounds is 80–100% and for third-generation compounds 90–100%.[27] Recent research has revealed an exceptionally low complication rate associated with the use of β-AAs in heart failure patients as well as perioperatively in high-risk cardiac patients.[142,173,179,225,231,254] Specifically, these studies do not report an increased number of episodes with severe hypotension, bradycardia or bronchospasm. Therefore, administration of β-AAs according to the reported dosing by Mangano and colleagues[142] and Poldermans and colleagues[173] does not require additional monitoring. Even when started acutely with high doses and in combination with potentially negative inotropic agents, β-AAs were well tolerated in compromised patients. Nonetheless, certain contraindications to β-AAs must be considered.

Haemodynamics

Excessive sympatholysis is undesirable in patients who depend heavily on central sympathetic tone for adequate circulatory function. While chronic administration of β-AAs improves systolic and diastolic function in heart failure patients,[73,115,228] acute exposure to β-AAs may lead to intolerable bradycardia and arterial hypotension and potentially result in an adverse outcome.[215] Accordingly, eye-drops with β-AAs were implicated in the progression of ischaemic optic nerve disorders and the progression of visual loss attributable to recurrent nocturnal hypotensive episodes.[89] Therefore, patients with advanced conduction defects or symptomatic bradycardia should not receive β-AAs without concomitant pacemaker therapy. However, patients with a resting heart rate below 60 beats min^{-1} may receive therapy with caution. One study evaluating the tolerability of β-AA titration in patients with idiopathic dilated cardiomyopathy found that generally accepted measures of the severity of heart failure were not predictive of problematic up-titration of β-AAs.[7] A low systolic blood pressure (<120 mmHg) was the strongest predictor of complications. The mechanisms underlying the good tolerability of initiation of β-AAs in patients with heart failure was previously investigated by Halpern and colleagues[81] (Fig. 5). Acute effects of metoprolol on systolic and diastolic function as well as on ventriculoarterial coupling were evaluated using volume–pressure loops. The results of these studies indicate that decreased afterload, as assessed by arterial elastance and the preservation of ventriculoarterial coupling and passive ventricular properties, explain the excellent tolerance of β_1-AR antagonists in heart failure patients (Fig. 5). Notably, β_1-AR antagonists also leave inotropic responses to β_2-AR receptors intact and thereby produce less cardiac depression and vasoconstriction. Conversely, studies using a pulmonary artery catheter technique showed an increase in systemic vascular resistance (SVR) after metoprolol administration in chronically treated, mostly NYHA III heart-failure patients.[123] Similarly, acute graded administration of esmolol in patients with severe ventricular dysfunction increased SVR to compensate for the decrease in cardiac output.[99] Intraoperatively, SVR decreases significantly during undisturbed anaesthesia, but increases markedly under surgical stimulation in metoprolol as well as placebo-treated patients.[139] However, SVR depends on loading conditions and contractility, which were not measured in all these studies. Therefore, SVR may not properly reflect the effects of β-AAs on distension in the arterial system, i.e. afterload. Accordingly, in mitral regurgitation-induced left ventricular dysfunction β-AAs decrease left atrial hypertension independently of changes in heart rate, which is thought to result from decreased afterload.[33 228]

Experience with recent large trials indicates that fewer than 5% of patients need to be withdrawn from β-AAs because of worsening heart failure when they are carefully monitored. The favourable haemodynamic effects and safety of perioperative β-AA administration is now also documented in several studies with brittle elderly surgical patients.[142 173 179 225 231 254] As the potentially adverse clinical effects of esmolol completely disappear within minutes of its discontinuation, current experience suggests the initiation and up-titration of this short-acting β_1-AR antagonist even in compromised patients perioperatively.[9]

Coronary vascular resistance

Sympathetic nerve stimulation in the presence of propranolol was reported to increase diastolic coronary resistance by 30%.[64] This coronary vasoconstriction is less likely to occur after administration of β_1-AR antagonists.[2] More importantly, in a study that measured simultaneously total coronary flow (sinus outflow) and local tissue flow (heated thermocouples), sympathetic stimulation after β-AA administration resulted in a decrease in sinus outflow but an increase in the nutritional microcirculatory flow.[107] This implies that a reduction in total coronary outflow does not necessarily parallel a decrease in tissue flow at the microcirculatory level. Also, the mechanism of the reduction in blood flow after administration of β-AAs is likely to be a result of decreased myocardial oxygen demand. This is strongly supported by the notion that atenolol decreases myocardial blood flow by 16% and increases coronary vascular resistance by 23%.[211] At the same time, however, the myocardial arteriovenous oxygen difference remains unaltered. Furthermore, when paced at the pre-atenolol heart rate, there is no decrease in coronary blood flow or increase in vascular resistance under atenolol treatment, which again clearly indicates that the observed decreases in coronary flow can be ascribed solely to decreased left ventricular work and myocardial oxygen demand. Adverse effects of β-AAs on feed-forward coronary vasodilation (mediated by β_2-ARs) clearly do not occur. Importantly, even in patients with vasospastic angina, administration of propranolol does not precipitate coronary spasms.[51]

Strategies to treat bradycardia and hypotension caused by β-adrenergic antagonists

In general, untoward circulatory effects can be treated easily with vagolytic drugs (atropine) or can be overcome pharmacologically with inotropic agents. If atropine is not effective in treating bradycardia, i.v. glucagon 2.5 μg kg^{-1} may be administered.[137 187] The haemodynamic improvements after glucagon treatment result mainly from its pronounced chronotropic effect. Importantly, β-adrenergic agonists are not the inotropic agents of choice in treating cardiac decompensation from β-adrenergic antagonism.[138] In the presence of fully established β-adrenergic antagonism, high doses of catecholamines, which significantly increase afterload and pulmonary artery pressure, have to be administered to overcome the receptor antagonism.[137 138 222] In metoprolol-treated patients, the response to phosphodiesterase III inhibitor (PDE3I) is superior to the response to dobutamine. Milrinone 25 μg kg^{-1} given over 10 min is well tolerated in patients with heart failure under carvedilol treatment and significantly improves the cardiac index with virtually no changes in heart rate and mean arterial pressure. PDE3Is retain their full haemodynamic effects in the face of β-adrenergic antagonism, because their site of action is beyond β-ARs. PDE3Is act specifically on the phosphodiesterase III isoenzyme, which is anchored to the sarcoplasmic reticulum.[246] Inhibitory effects on degradation of cAMP remain compartmentalized and thereby lead selectively to increased activity of sarcoplasmic reticulum PKA, which preferentially improves systolic and diastolic function.[129] Notably, the combination of glucagon and milrinone effectively restores cardiac output, but may increase heart rate excessively.[187] Interestingly, the combination of PDE3I and β-AA, administered on a short- or long-term basis, confers additive beneficial but subtractive adverse effects (Table 6).[197] Accordingly, concomitant administration of PDE3Is was used to improve the tolerability of starting β-adrenergic antagonism in patients with severe heart failure by counteracting the myocardial depressant effect of adrenergic withdrawal. The results of these studies suggest that the combined treatment may have beneficial effects beyond those produced by β-AAs. Similarly, the use of prophylactic concomitant PDE3I administration may have the potential to facilitate the introduction of acute preoperative β-adrenergic antagonism. Along with their favourable effects on cardiac function, PDE3Is also partially activate protein kinase G in bronchial smooth muscle, counteracting the bronchoconstriction of β-AAs. In the future, adverse negative inotropic effects of β-AAs may be reversed by the transient use of Ca^{2+} sensitizers, which are currently under investigation.[194]

Management of acute poisoning with β-adrenergic antagonists

Most poisoning is uneventful, but serious effects of agents with membrane-depressant effects, such as propranolol and oxprenolol, have been reported.[41] In very high doses, respiratory and cardiovascular depression occurs and artificial ventilation may be necessary.[218] Insulin improves survival in a canine model of acute β-AA toxicity and seems to be a better antidote than glucagon or epinephrine.[114] In an animal model of spontaneously breathing rats and propranolol intoxication, administration of catecholamines (dopamine and isoprenaline) significantly reduced survival time.[218] Importantly, an effect of extracellular ions on β-

AA cardiotoxicity had been described.[113] Low extracellular K^+ and high extracellular Na^+ may reverse refractoriness to pacing associated with atenolol and propranolol, which is consistent with the hypothesis that β-AA toxicity is mediated by membrane hyperpolarization.

Drug interactions and the withdrawal phenomenon

Concurrent administration of β-AAs with drugs that alter gastric, hepatic or renal function may affect the blood levels, duration of action and efficacy of β-AAs. In general, doses of lipophilic β-AAs must be reduced in the presence of liver dysfunction, whereas doses of hydrophilic β-AAs need to be adjusted in renal dysfunction. Although lipophilic substances generally have larger volumes of distribution, they usually have shorter plasma elimination half-lives because of the greater capacity for drug clearance by the liver than the kidneys. Polymorphic metabolism of β-AAs is of clinical relevance. In particular, lipophilic β-AAs are metabolized by oxidative pathways and glucuronidation, and oxidative clearance is influenced by the debrisoquine hydroxylation gene.[104 201 203] Poor metabolizers with polymorphic variants of cytochrome P450 may therefore have increased plasma levels. Also, changes in metabolism related to the genetic background appear to be responsible for decreased efficiency of β-AAs in black patients. Notably, bisoprolol is independent of any genetic polymorphism of oxidation.[131]

Concomitant administration with Ca^{2+} channel blockers results in additive myocardial depression, and QT prolongation may occur with hypokalaemia, particularly if treatment with β-AAs is associated with the use of diuretics.[118] Sinus arrest and atrioventricular block were described under combined administration of diltiazem and β-AAs, but this seems to occur only rarely.[156] A combined infusion of nifedipine and metoprolol has been used successfully in patients undergoing CABG surgery.[172] Importantly, sinus node dysfunction may be further enhanced by digoxin, guanidine, procainamide, disopyramide, methyldopa, reserpine, clonidine, cimetidine, lithium and lidocaine. The practice of concomitant amiodarone and β-AA treatment is not hazardous.[20] However, the potential for conduction abnormalities and arterial hypotension must be considered carefully.

In patients receiving β-AAs, the duration of regional anaesthesia is prolonged by 30–60% after administration of local anaesthetic containing epinephrine.[256] Severe complications were reported in cancer patients receiving β-AA treatment after administration of aminoglutethimide as a hormonal cancer therapy.[85] Although the novel ultra-short-acting opioid remifentanil is metabolized by the same non-specific esterases in the blood as esmolol, there is no apparent pharmacokinetic interaction between remifentanil and esmolol in a rat model.[83] Importantly, the use of non-steroidal anti-inflammatory drugs offsets the antihypertensive effects of β-AAs.[57] Carvedilol may increase plasma levels of digoxin by 15%. Conversely, the bioavailability of digoxin may be decreased after oral administration of talinolol, a β_1-AR antagonist, as a result of competition for intestinal P-glycoprotein between digoxin and talinolol.[235] Interference of propofol and volatile anaesthetics with β-adrenergic signal transduction has been reported and may modulate the response to β-AAs.[86 253 259]

When combining α_2-agonists and β-AAs, the following issues need to be addressed. Concomitant administration of sotalol and clonidine produces an increase in blood pressure. Conversely, propranolol potentiates clonidine-induced decreases in blood pressure, which is even more pronounced with atenolol.[135] Special caution must be used in treating withdrawal syndromes from α_2-agonists, as α_2-agonists and β-AAs cannot be used interchangeably. Whereas clonidine successfully blunts β-AA withdrawal, β-AA substitution in clonidine withdrawal provokes hazardous hypertension.[106] Abrupt autonomic changes occur with β-AA withdrawal, and sudden cardiac death may occur.[223 230] This withdrawal phenomenon is virtually absent in β-AAs with intrinsic sympathetic activity. Importantly, inadvertent withdrawal, particularly from hydrophilic β-AAs, must be considered after massive intraoperative transfusion. Although ACE inhibitors may induce catecholamine-resistant intraoperative hypotension, preoperative withdrawal of ACE inhibitors may lead to decreased β-AR responsiveness and down-regulation.[247]

Renal function

In general, β-AAs decrease renal blood flow and glomerular filtration rate as a result of decreased cardiac output.[11] However, this is not of clinical significance, and most β-AAs, particularly the β_1-AR antagonists, alter renal haemodynamics only slightly. β-AAs reduce tubular reabsorption of fluid and electrolytes leading to reduced sodium and water retention, while renal function is well maintained.[169 213] This effect is beneficial, particularly in the perioperative period. Very few cases of clinically evident deterioration in patients with already impaired renal function have been reported.

Pulmonary function

Chronic obstructive pulmonary disease is not a contraindication for perioperative β-adrenergic antagonism, and even patients with inactive stable asthmatic disease might be given a trial of a low dose of a highly selective β-AA with appropriate ancillary properties [nebivolol (NO release), celiprolol (β_2 stimulation), bisoprolol].[35] However, patients with active asthma and a demonstrable bronchodilator response should not receive β-AAs. Celiprolol (200 mg day^{-1}) and atenolol (25 mg day^{-1}) can be used relatively safely in stable asthmatic patients, while metoprolol significantly increases airway resistance.[214] Albuterol administered as four puffs before tracheal intubation blunts airway response significantly in patients with reactive airway disease and should be used prophylactically in these patients.[149] Interestingly, β-AAs increase hypoxic pulmonary vasoconstriction, which may be favourable in patients undergoing one-lung ventilation.[24]

Metabolic changes associated with β-adrenergic antagonists

Several large studies indicate that there is some hyperglycaemic effect in patients receiving β-AAs.[77] However, as pointed out earlier, this is not a reason to withhold β-AA treatment. Early treatment of myocardial infarction with β-AAs results in a 13% reduction in mortality in all patients compared with a 37% reduction in diabetic patients.[117] Similarly, reinfarction is reduced by 21% in patients without diabetes compared with 55% in diabetic patients.[80] Nonetheless, β-AAs impaired glucose tolerance and appeared to increase the risk of diabetes on a long-term basis by 28% in a recent study.[77] Other studies (atenolol, acebutolol) did not show an increased risk of hyperglycaemia or diabetes in subjects taking long-term β-AA treatment.[162 188] Importantly, prolonged hypoglycaemia with delayed recovery may complicate β-AA treatment in diabetic patients, particularly those with non-insulin-dependent diabetes mellitus.[50] Sweating, but not tachycardia or palpitations, may be present in hypoglycaemic episodes.[229] Also, diastolic blood pressure may be increased significantly as a result of unopposed epinephrine-induced α-AR stimulation. Hypoglycaemia as a complication of β-AA therapy is virtually absent with β-AAs that have intrinsic sympathetic activity.

Although not of immediate concern in the perioperative period, unfavourable changes in lipid metabolism have been reported with β-AA treatment. β_1-AR antagonists and labetalol do not increase triglycerides but may elevate very low density lipoproteins.[49] Atenolol does not affect high-density lipoproteins, whereas metoprolol decreases them.[185] However, total cholesterol, is largely unaffected by β-AA treatment and a myriad of clinical and experimental studies document the anti-atherosclerotic effect of β-AAs

Cognitive dysfunction

The association between β-adrenergic antagonism and depression remains controversial. More recent studies did not find any relationship between β-AA use and depression or cognitive impairment.[23 53] However, sleep disturbances, difficulty in falling asleep and vivid dreams with nightmares are clearly associated specifically with the use of lipophilic β-AAs.

Vascular complications

Large studies on patients with peripheral occlusive artery disease do not show any adverse effects of β-AAs on walking capacity or symptoms of intermittent claudication, even in patients with severe disease.[180] Also, β-AAs do not increase vascular complications in these patients.[87] Because of epinephrine-induced effects mediated by the β_2-AR, the administration of β_1-AR antagonists may even result in decreased arterial resistance, which may increase nutritive blood flow.

Conclusions

The collective interpretation of the experimental and clinical data summarized here is that the consistently demonstrable beneficial effects of β-adrenergic antagonism on the cardiovascular system, as well as on stress acting through the nervous system, translates into favourable changes in outcome. β-Adrenergic antagonism should therefore be employed more generously in the stressful perioperative period. Many favourable effects on the biology of cardiomyocytes are closely related to bradycardia. By cautious dose titration and selection of a highly specific β_1-AA, the majority of patients, even those with impaired ventricular function, can be started safely on β-AAs and up-titrated successfully to cardioprotective doses. However, β-AAs with strong inverse agonism should be avoided in these patients. Diabetes and chronic obstructive pulmonary disease are not contraindications to perioperative β-AA therapy. Patients with obstructive pulmonary disease should be treated with a highly selective β_1-AA with bronchodilating ancillary properties (β_2-adrenergic agonism, NO release). Many important questions regarding the optimal drug profile of β-AAs for specific patient sub-populations and the optimal dosing and duration of perioperative β-AA treatment remain to be addressed in future studies. For improved safety, the potential benefit of combined treatment with β-AAs and PDE3Is should be evaluated in severely compromised patients. If we accept that β-AAs act on fundamentally detrimental biological processes, we will use them more comfortably perioperatively.

Addendum

During the review process of this article, two important studies concerning perioperative β-AAs were published and need consideration.[263 264] Poldermans and colleagues reported that postoperative continuation and up-titration of perioperative bisoprolol treatment enhanced the protective effects in the study population described previously.[173] Most of the effect was observed in the first 6 months after surgery and was preserved over the following 2 yr. Therefore, combined perioperative and long-term bisoprolol treatment leads, in this highly selected patient population, to a reduction of more than 50% in cardiovascular morbidity and mortality.

Using a retrospective and non-randomized approach, Boersma and colleagues[264] investigated 1351 consecutive vascular patients to assess the relationship between clinical characteristics, dobutamine stress echocardiography, β-AA therapy and perioperative cardiac events. The reported cardiac complication rates were greatly reduced in most patient categories (98% of patients) by β-AA treatment. Only 2% of patients with three and more risk factors (age >70 yr, current angina, prior myocardial infarction, congestive heart failure, prior cerebrovascular accident, diabetes and renal failure) and extensive dobutamine stress echocardiography-induced ischaemia (at least five segments) would not profit from β-AAs.

These studies thus support the conclusion that perioperative β-adrenergic antagonism is likely to improve long-term outcome in selected groups of patients with or at risk of coronary artery disease.

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BJA

SHORT COMMUNICATIONS

Optimizing fluid therapy in mechanically ventilated patients after cardiac surgery by on-line monitoring of left ventricular stroke volume variations. Comparison with aortic systolic pressure variations

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Background. Mechanical ventilation causes changes in left ventricular preload leading to distinct variations in left ventricular stroke volume and systolic arterial pressure. Retrospective off-line quantification of systolic arterial pressure variations (SPV) has been validated as a sensitive method of predicting left ventricular response to volume administration. We report the real-time measurement of left ventricular stroke volume variations (SVV) by continuous arterial pulse contour analysis and compare it with off-line measurements of SPV in patients after cardiac surgery.

Methods. SVV and SPV were determined before and after volume loading with colloids in 20 mechanically ventilated patients.

Results. SVV and SPV decreased significantly after volume loading and were correlated (r=0.89; P<0.001). Changes in SVV and changes in SPV as a result of volume loading were also significantly correlated (r=0.85; P<0.005). Changes in SVV correlated significantly with changes in stroke volume index (SVI) (r=0.67; P<0.005) as did changes in SPV (r=0.56; P<0.05). SVV determined before volume loading correlated significantly with changes in SVI (R=0.67; P <0.005). Using receiver operating characteristics curves, the area under the curve was statistically greater for SVV (0.824; 95% confidence interval: [CI] 0.64–1.0) and SPV (0.81; CI: 0.62–1.0) than for central venous pressure (0.451; CI: 0.17–0.74).

Conclusions. Monitoring of SVV enables real-time prediction and monitoring of the left ventricular response to preload enhancement in patients after cardiac surgery and is helpful for guiding volume therapy.

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Keywords: heart, left ventricular preload; heart, left ventricular response; heart, systolic pressure variation; heart, central venous pressure; measurement techniques, pulse contour analysis; monitoring, haemodynamic

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Correct assessment of hypovolaemia and the decision to undertake volume resuscitation is often difficult to make clinically. This is especially so in critically ill patients with compromised myocardial or pulmonary function, or with systemic inflammation from sepsis or cardiac surgery using cardiopulmonary bypass. In these patients, an adequate preload is of utmost importance for optimizing cardiac performance and organ perfusion. Positive airway pressures produced by mechanical ventilation are known to cause intermittent changes in biventricular preload which lead to distinct left ventricular stroke volume variations (SVV) and, in consequence, to systolic arterial pressure variations (SPV).[1] Excessive SPV, visible as undulations in the arterial pressure curve trace, are a well recognized clinical sign of

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hypovolaemia. As demonstrated in earlier investigations, off-line quantification of SPV is a sensitive method of predicting left ventricular response to volume administration.[2 3] Nevertheless, real-time and continuous quantification of SPV has not been determined. Arterial pulse contour analysis, which has been clinically validated for continuous cardiac output measurement,[4] now enables continuous quantification of real-time SVV, which causes SPV. Berkenstadt and colleagues recently reported measurement of SVV to predict fluid responsiveness in patients undergoing brain surgery.[5] However, to our knowledge, there are no published data on a comparison of SVV and SPV.

We investigated the relation between SVV and the haemodynamic response of the left ventricle to volume loading compared with the SPV determined off-line in 20 mechanically ventilated patients after cardiac surgery using cardiopulmonary bypass.

Methods and results

With the approval of the local institutional ethics committee and informed consent, 20 patients were studied after elective cardiac surgery. Prior to surgery, each patient had a central venous catheter and a 4F thermistor-tipped arterial catheter (PV 20L16, Pulsion Medical Systems AG, Munich, Germany) inserted into the femoral artery and advanced into the distal abdominal aorta. This catheter was connected to a bedside haemodynamic monitor for arterial pulse contour analysis (PiCCO 4.1, Pulsion Medical Systems AG, Munich, Germany). Cardiac output and stroke volume were measured by the transcardiopulmonary thermodilution technique (performed in triplicate).[4] Raw data were indexed using the body surface area to calculate thermodilution stroke volume index (SVI). After initial calibration of the arterial pulse contour cardiac output by thermodilution, cardiac output, pulse contour cardiac output and pulse contour stroke volume were recorded continuously. SVV, demonstrating the variations in the beat-to-beat stroke volume around the mean during the respiratory cycle, was assessed using an algorithm that utilizes a continuously sliding time window of 30 s to calculate the mean stroke volume. This time window was divided into four periods of 7.5 s; within each window, the highest and the lowest value of stroke volume were used to calculate SVV.

For the off-line calculation of SPV, we recorded the digitalized trace of the arterial pulse wave on a computer connected to the haemodynamic monitor. We used the same individual time window of 30 s divided into four periods of 7.5 s, which was analysed for the corresponding value of SVV and determined the highest and lowest value of systolic arterial pressure to calculate SPV.

Drug therapy was not changed within the study period. After recording of central venous pressure, thermodilution SVI and SVV, and a recording of the arterial pressure curve trace for later determination of SPV, volume loading was performed over 10 min using 3.5% oxypolygelatine 20 ml × body mass index (mean 548 ml). The measurements were then repeated.

Statistical analysis of the data was performed on a standard personal computer using SPSS for Windows 10.0 run under Windows NT. All variables are expressed as mean (SD). Correlation of haemodynamic variables and their changes were assessed using Pearson's correlation. Receiver operating characteristics (ROC) curves were calculated with varying discriminating thresholds for each variable to assess the ability to predict volume responsiveness.[6]

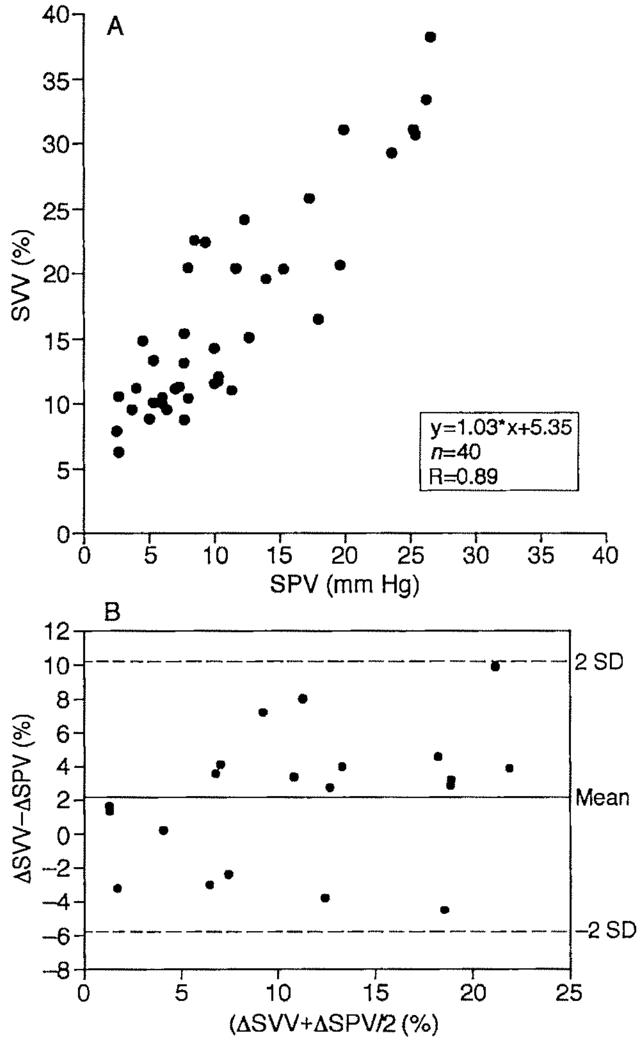

Fig 1 (A) Linear regression analysis of the relationship between systolic arterial pressure variations (SPV) obtained by off-line analysis of the trace of the arterial pressure wave form (*x*-axis), and the left ventricular stroke volume variations (SVV) obtained by real-time continuous arterial pulse contour analysis (*y*-axis) (B) Differences between the changes in SVV (ΔSVV) and the changes in SPV (ΔSPV) plotted against the average of each pair of values according to Bland and Altman[7] The *x*-axis shows the mean of ΔSVV by pulse contour analysis and ΔSPV by off-line analysis of the arterial pressure curve trace The *y*-axis shows the mean (2SD) difference between the two methods

All patients tolerated the study treatment well. Overall, the thermodilution SVI increased from 40 (9) ml m^{-2} to 50 (9) ml m^{-2}, whereas SVV decreased from 23 (7) to 11 (3)%, and SPV from 16 (7) to 6 (3) mm Hg. Central venous pressure increased significantly from 7 (2) to 10 (3) mm Hg. Linear regression analysis of SVV and SPV is shown in Figure 1A (R=0.89; P<0.001). Changes (%) in SVV (ΔSVV) and SPV (ΔSPV) as a result of volume loading correlated significantly (R=0.85; P<0.005). Comparison of ΔSVV and ΔSPV using a Bland–Altman plot is shown in Figure 1B.[7] Changes in thermodilution SVI (ΔSVI) correlated significantly with ΔSVV (R=0.67; P<0.005) and ΔSPV (R=0.56; P<0.05). To investigate the ability of each variable to predict volume responsiveness, ΔSVI was correlated with values of SVV determined before volume loading (r=0.67; P<0.005), as well as with values of SPV before volume loading (r=0.60; P<0.01). ROC curves for central venous pressure, SPV and SVV were generated with varying discriminating thresholds for each variable. Patients were classified as responders to volume loading if the increase in SVI was >15% (n=13), or as non-responders (n=7), according to Stetz *et al.*[8] When comparing the areas under the ROC curves, the area for SVV (0.83; 95% confidence intervals [CI]: 0.64–1.0) and SPV (0.81; CI: 0.62–1.0) did not differ significantly, whereas the area for central venous pressure (0.42; CI: 0.17–0.74) was significantly smaller (P<0.001).

Comment

These results primarily demonstrate the ability of continuous and real-time measurement of SVV by arterial pulse contour analysis to predict and assess the left ventricular response to volume loading in cardiac surgery patients. So far, directly accessible information on whether the sarcomeres of the left ventricle are still in the volume-dependent part of the Starling curve or have already reached their optimal fibre length (the latter describing 'preload' in the pure physiological sense),[9] cannot be provided by routine clinical monitoring. SPV and its retrospective off-line quantification for assessment of volume dependency has been validated,[2 3] as have arterial pulse pressure changes.[10] The technique of arterial pulse contour analysis enables us to quantify reliably the underlying SVV causing SPV and pulse pressure changes. Moreover, this is possible by an on-line technique using SVV as a continuous bedside variable. As demonstrated here, SVV offers continuous unique functional data on the patient's individual myocardial Starling curve and preload status, and thus enables prediction of volume responsiveness and monitoring of the effect of fluid loading. SVV is therefore a clinically useful and feasible bedside device for real-time functional preload monitoring in cardiac surgery patients.

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Reliability of epigastric auscultation to detect gastric insufflation

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Background. We studied the reliability of epigastric auscultation to detect gastric insufflation in 30 anaesthetized, paralysed intubated patients.

Methods. A 16FG gastric tube was positioned with the tip in the mid-oesophagus with the proximal end attached to an injection port with a one-way valve. Four observers participated in the study. Observers were paired and each pair studied 15 patients. Each patient underwent four test sequences in random order, two by each observer. Each test sequence comprised one observer injecting different volumes of air (0.25 ml, 0.5 ml, 1 ml, 2 ml, 3 ml, 4 ml, 5 ml, 10 ml, 15 ml and 0 ml as a control) in random order whilst the second blinded observer listened with a stethoscope over the epigastrium. Each randomized volume was injected rapidly at 5 s intervals for 1 min. The number of injections required to detect air entering the stomach was recorded. The stomach was deflated between each test sequence.

Results. To detect air entering the stomach with 95% confidence, 11 injections were required for 0.25 ml; 7 for 0.5 ml; 3 for 1 ml; 2 for 2 ml and 3 ml, and 1 for ≥4 ml. The mean (range) inter- and intraobserver reliability was 0.73 (0.71–0.75) and 0.76 (0.76–0.89), respectively. The incidence of false positives was 21% (25/120) and the incidence of false negatives was 10% (103/1080), making the specificity and sensitivity 79% and 91%, respectively.

Conclusions. We conclude that epigastric auscultation can detect gastric insufflation of 0.25 ml air after 11 breaths and ≥4 ml air after one breath with 95% confidence. Inter- and intraobserver reliability is moderate to excellent. Epigastric auscultation should be repeated to reduce the risk of false positives.

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Keywords: complications, gastric insufflation; ventilation, positive pressure

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Gastric insufflation is a major hazard of positive-pressure ventilation in non-intubated patients and can predispose to regurgitation, impaired ventilation, reduced cardiac output and visceral rupture.[1] In a survey of almost 40 000 general anaesthetics, 15% were with positive-pressure ventilation using the laryngeal mask airway (LMA†)[12] and gastric insufflation has been reported in this context.[3] Epigastric auscultation is a clinical test commonly used to detect air entering the stomach during positive-pressure ventilation and it has been suggested that volumes of as little as 5 ml can be detected,[4] but this has not been formally tested. We determined the reliability of epigastric auscultation to detect gastric insufflation.

Methods and results

With ethics committee approval and written informed consent, we studied 30 ASA I–II adult patients requiring tracheal intubation for elective surgical procedures in the supine position. Patients were excluded if they were pregnant, had a body mass index >35 kg m^{-2} or had oesophagogastric disease. Anaesthesia was induced with fentanyl 1 μg kg^{-1} and propofol 2 mg kg^{-1} and maintained with 1–3% sevoflurane in 100% oxygen. Muscle relaxation was with rocuronium 0.5 mg kg^{-1}. After laryngoscope-guided tracheal intubation, a 16FG gastric tube was

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positioned in the oesophagus by feeding the tip 10 cm beyond the upper oesophageal sphincter using Magill's forceps. The proximal end of the gastric tube was attached to an injection port with a one-way valve so that known volumes of air could be injected. Pre-prepared syringes were used to inject the following volumes (syringe size): 0.25 ml (1 ml), 0.5 ml (1 ml), 1 ml (1 ml), 2 ml (3 ml), 3 ml (3 ml), 4 ml (5 ml), 5 ml (5 ml), 10 ml (10 ml) and 15 ml (20 ml). A sham injection of 0 ml functioned as a control. Four observers (A, B, C and D) participated in the study. Observers were paired (A with B, C with D) and each pair studied 15 patients. To determine inter- and intraobserver variation, each patient underwent four test sequences in random order, two by each observer. Each test sequence comprised one observer injecting each of the nine volumes plus the sham volume in random order whilst the second blinded observer listened with a stethoscope over a fixed location 5 cm inferolateral to the xiphisternum. Each randomized volume was injected rapidly at 5 s intervals for 1 min or until the blinded observer indicated that air had entered the stomach. The observer was verbally notified immediately before each injection. Observations were made when the operating theatre was quiet, before or after surgery. The time when air was first heard entering the stomach was recorded. The observer injecting air noted if there were any oropharyngeal leaks during each injection by listening over the mouth. At the end of each test sequence, the stomach was deflated by advancing the gastric tube 30 cm into the stomach, applying suction, and withdrawing it 30 cm. Blinding was accomplished by a large opaque drape separating the two observers.

Sample size (n=30) was based on data from a pilot study with eight patients with an injected volume of 0.5 ml (reporting a difference of the mean of 1.5 and a SD of 2.7) for a type I error of 0.05 and a power of 0.9. The distribution of data was determined using Kolmogoroff–Smirnov analysis.[5] Inter- and intraobserver reliability was analysed using intraclass correlation coefficient (ICC).[6] Scores for statistical measurements with the ICC range from 0 to 1 where 0 shows no reliability and 1 shows perfect reliability. A score $\geq$0.75 is graded as excellent reliability, 0.41–0.74 as moderate reliability and <0.40 as poor reliability.[7]

The mean (range) age, height and weight were 38 (18–81) yr, 172 (151–193) cm and 69 (48–110) kg, respectively. The male:female ratio was 16:14. There were no missing data points. To detect air entering the stomach with 95% confidence, 11 injections were required for 0.25 ml; 7 for 0.5 ml; 3 for 1 ml; 2 for 2 ml and 3 ml; and 1 for $\geq$4 ml. The interobserver reliability between A and B was 0.71 and between C and D was 0.75, with an overall reliability of 0.73. The intraobserver reliability was 0.89, 0.76, 0,76 and 0.76 for observer A, B, C and D, respectively, with an overall value of 0.76. The incidence of false positives was 21% (25/120) and the incidence of false negatives was 10% (103/1080), making the specificity and sensitivity 79% and 91%, respectively. The incidence of false negatives for volumes $\geq$4 ml after one breath was 4% (16/360) and 0% after four breaths. No oropharyngeal leaks were detected.

Comment

We found that epigastric auscultation is a reliable technique for detecting gastric insufflation. It is more reliable than chest auscultation in detecting the position of a double-lumen tube[8] and in assessing breath sounds,[9] but less reliable than neck stethoscopy for detecting oropharyngeal leak of gas during positive-pressure ventilation with the LMA.[10] Our finding that $\geq$4 ml air can be detected after one injection with 95% confidence is similar to the figure of 5 ml alluded to by Lawes *et al.*[4] The smaller the volume of air entering the oesophagus, the greater the number of injections required before detection. We speculate that gas accumulates in the oesophagus and then vents into the stomach once a critical volume is reached. Our data suggest that this critical volume is 3–4 ml. If true, volumes smaller than 0.25 ml should be detectable provided adequate listening time is allowed. We found that inter- and intraobserver reliability was moderate to excellent. One individual had a higher intraobserver variability (0.89) than the others, suggesting that some individuals are better at detecting gastric insufflation than others. Interestingly, we detected no oropharyngeal leaks during the test sequence. This suggests that once air enters the oesophagus in anaesthetized paralysed patient it tends to enter the stomach.

Our experimental model does not precisely mimic the clinical situation in which gastric insufflation occurs because patients were intubated and a gastric tube was *in situ*. However, tracheal intubation was necessary for airway protection and to ensure that no additional air leaked into the oesophagus, as might have occurred if a face mask or LMA was used. The gastric tube was necessary to allow known volumes of air to be injected into the oesophagus. Although unlikely, it is also possible that the gastric tube may have interfered with the dynamics of the lower oesophageal sphincter and thus influenced the quality of sound generated as air passed across it into the stomach.

We found a false-positive rate of 21% and a false-negative rate of 10%. This implies that in approximately one in five occasions the clinician will hear air entering the stomach when in fact it is not, and in approximately 1 in 10 occasions will not hear air entering the stomach when in fact it is. Repeated auscultation is likely to reduce the false-positive rate. The clinical importance of small volumes of air entering the stomach with every breath is unknown. We speculate that the healthy stomach will be able to cope with some gas load without insufflation through absorption and movement of the gas into the small bowel. Cricoid pressure is an effective method of preventing gastric insufflation during ventilation with the face mask and probably with other extraglottic airway devices.[1]

We conclude that epigastric auscultation can detect gastric insufflation of 0.25 ml air after 11 breaths and

≥4 ml air after one breath with 95% confidence. Inter- and intraobserver reliability is moderate to excellent. Epigastric auscultation should be repeated to reduce the false-positive rate.

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Deep topical fornix nerve block versus peribulbar block in one-step adjustable-suture horizontal strabismus surgery

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Background. We compared the efficacy of deep topical fornix nerve block anaesthesia (DTFNBA), which does not paralyse the extraocular muscles, with peribulbar block in patients undergoing one-step adjustable-suture horizontal strabismus surgery. Patients with a vertical, oblique squint were excluded from the study.

Methods. We studied 100 patients, allocated randomly to two groups. Group 1 (n=50) received peribulbar block with 5 ml of 1:1 mixture of 0.5% plain bupivacaine and 2% lignocaine supplemented with hyaluronidase 300 i.u. ml^{-1}. Group 2 (n=50) received DTFNBA with placement of a sponge soaked in 0.5% bupivacaine deep into the conjunctival fornices for 15 min. No sedation was given to either group. Analgesia was assessed by direct questioning of patients during the procedure. A three-point scoring system was used (no pain =0, discomfort =1, pain =2). If the pain score was 1, the patient was asked to look in the opposite direction to decrease the tension on the periosteal attachment of the muscle to relieve discomfort. If the pain score was 2 at any stage of the operation, general anaesthesia was given.

Results. In Group 2, significantly more patients (15) experienced discomfort than in Group 1 (no patients) (P<0.05), but general anaesthesia was not needed.

Conclusions. DTFNBA is a useful technique for intraoperative adjustable-suture strabismus surgery. It does not alter muscle tone, thus allowing the surgeon to adjust the muscle sutures intraoperatively, and reducing the incidence of under- or over-correction of the squint in the immediate postoperative period.

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In this study, we compared deep topical fornix nerve block anaesthesia (DTFNBA) as described by Rosenthal,[1] with peribulbar nerve block in patients undergoing one-step adjustable-suture strabismus surgery. Using adjustable sutures during strabismus surgery allows the ophthalmic surgeon to prevent over- or under-correction of the squint in the postoperative period.[2] Adjustable sutures can be attached to one or more ocular muscles. If the alignment is not satisfactory at the end of surgery, one or more of the muscles can be moved to a new position to produce the optimal alignment. This suture adjustment is usually performed within 24 h of the initial surgery.

The popularity of the adjustable-suture technique was the stimulus for introducing the use of topical anaesthesia in strabismus surgery.[3] Unlike general anaesthesia and regional block techniques in eye surgery, DTFNBA avoids prolonged recovery of the eye muscles from motor block and allows suture adjustment at the time of surgery (rather than within the next 24 h), in what we call one-step adjustable-suture strabismus surgery. When adjustable sutures are used intraoperatively in co-operative fully alert patients who have received DTFNBA, the patient can move their eyes freely. Thus, the alignment of the eyes can be fully assessed at the time of surgery instead of postoperatively, as in the standard technique.

Methods and results

One hundred patients scheduled for elective adjustable horizontal strabismus surgery were enrolled in the study after we had obtained approval from the institutional ethics committee and patient consent. We estimated our sample size on the basis of the method described by Lerman.[4] A sample size of 45 can detect a 20% difference between each group; this will give an alpha value of 0.05 with a power of 80%. With a fall-out rate of approximately 10%, we decided to increase the number of patients in each group to 50. All patients had been assessed as suitable for a regional block technique and were not premedicated. Patients were allocated randomly to one of two groups (closed-envelope method): Group 1 (n=50) received peribulbar block. Group 2 (n=50) received DTFNBA. The axial length (the distance from the cornea to the retina) is usually measured using the axial length scanner. If the axial length is 26 mm or longer, the globe is elongated. Patients with an elongated globe were omitted from the study because of an increased risk of globe perforation if peribulbar block is used.[5] Patients with a vertical, oblique squint (which is less common) were also excluded because access to the muscles surgically is more difficult. Children and uncooperative patients were excluded from the study.

Before the block, a peripheral vein was cannulated, and heart rate and oxygen saturation were monitored; arterial pressure was monitored non-invasively. In both groups, the conjunctival fornices were first anaesthesized with local anaesthetic drops (0.4% oxybuprocaine).

All peribulbar blocks were performed by the same person by single inferotemporal injection of 5 ml of a 1:1 mixture of 0.5% plain bupivacaine and 2% plain lidocaine supplemented with hyaluronidase, 300 i.u. ml^{-1}, using a 5 ml syringe and a 25 gauge, 25 mm long disposable needle.[6 7] With the gaze fixed straight ahead in the primary position, the injection site was identified at the junction of the lateral one-third and medial two-thirds of the inferior orbital rim. The direction of the needle was slightly medial and cephalad. The local anaesthetic was injected slowly over a period of 1 min. To ensure complete paralysis of the eye before starting surgery, another medial injection of 3 ml of the same local anaesthetic mixture was given transconjunctivally with a 30 gauge, 25 mm needle on the medial side of the caruncle, at the extreme medial side of the palpebral fissure.

DTFNBA was performed using two 2×3 mm sponges cut from the tip of a Microsponge™ (regular tip) (Alcon® surgical), soaked with 0.5% bupivacaine, applied deep into the conjunctival fornices.[1 8] The sponges were removed after 15 min. The surface anaesthetic effect was tested by grasping the limbus with Castroviejo 0.12 tissue forceps.

A simple pain scoring system was used for both groups: no pain=0, discomfort=1, pain=2. Scoring was performed at several stages of the operation: conjunctival incision, muscle hooking, muscle suture, muscle cutting, scleral suture, and conjunctival suture. If the pain score was 1, the patient was asked to look in the opposite direction to decrease the tension on the periosteal attachment of the muscle and relieve the discomfort. If the pain score was 2 at any stage of the operation, general anaesthesia was given.

In Group 2 (DTFNBA), following correction of the muscle, the patient was asked to sit up and sterile spectacles were applied. Spectacles were sterilized by soaking then in Alkanol for 7 min (100 g Alkanol contains 70.5 g isopropanol, 0.05 g chlorhexidine digluconate and 30% hydrogen peroxide solution). The amount of optical correction induced was observed. If the correction was unsatisfactory, the tuck or recession on the muscle was changed until the correction was satisfactory. The final knots were tied and the conjunctiva secured. A combined antibiotic—steroid ointment was applied, and the eyes left uncovered.

Parametric data were analysed using Student's *t*-test; non-parametric data were compared using the Mann–Whitney test. A *P* value of <0.05 was considered statistically significant.

There was no significant difference between the patient characteristics of the two groups (Table 1).

In Group 1, the pain score was 0 at all stages while operating on the medial and lateral recti. In Group 2, the pain score was 0 at all stages while operating on the lateral recti. When operating on the medial recti, 15 patients experienced discomfort during muscle hooking ($P<0.05$), which disappeared on asking the patient to abduct their eyes when slight backward pressure on the globe (retropulsion) was applied. These procedures relax the muscle and decrease the tension on the periosteal insertion of the muscle. No patient in either group experienced pain at any other stage of the operation. The number of patients in each group with each pain score at the various stages of surgery on the medial recti is shown in Table 2.

Comment

In order to improve the success rate of surgical correction of strabismus in young and adult patients, different techniques using adjustable sutures have been described.[2] These suture adjustments are usually performed within 24 h of the initial surgery. Although readjusting the sutures in this way helps to improve the success rate of strabismus surgery, it may have disadvantages. Tissue oedema around or within the muscle to be adjusted may make the procedure difficult. In addition, the patient may be reluctant to undergo another procedure, and there may be operative complications such as suture slippage and suture breakage, all of which require return to the operating room for full exploration.[9] Even after full adjustment, a residual over- or under-correction may still be present and necessitate another surgical procedure. We therefore decided to perform one-step adjustable-suture strabismus surgery under DTFNBA to improve the overall success rate in young and adult patients and to avoid the disadvantages of readjusting the sutures within 24 h of surgery.

Table 1 Patient characteristics in the two groups. There were no significant differences between groups

	Group 1 (peribulbar block)	Group 2 (DTFNBA)
Men/women (*n*)	30/20	35/15
Mean age (range) (yr)	25 (18–37)	24 (19–38)
Mean weight (SD) (kg)	75 (11.4)	68 (10.8)
ASA I (*n*)	50	50

Although most ophthalmic surgeons believe that pain in squint surgery results from pulling on a muscle, studies have proved that this is not altogether true. Pain also results from the retraction of an extraocular muscle causing traction on the pain-sensitive periosteum at the muscle origin.[10] In group 2 (DTFNBA), we found that hooking a horizontal extraocular muscle (i.e. lateral or medial rectus) is much less painful if the patient is asked to look in the opposite direction to the hooked muscle. This causes relaxation of the muscle to be hooked so that traction on the periosteum is less, with less discomfort. In all our patients, hooking of the lateral rectus muscle was simple and painless, whereas hooking of the medial rectus muscle resulted in discomfort in 15 patients. The line of pull of the medial rectus is straighter than that of the lateral rectus because the arc of contact of the lateral rectus with the globe is greater. In addition, there is an attachment between the medial rectus sheath and the pain-sensitive meninges around the optic nerve, but there is no such attachment in the lateral rectus. The absence of fascial attachments between the medial rectus and other muscles also results in a more direct pull on the periosteum. Slight backward pressure on the globe (retropulsion) with active abduction of the eye while hooking the medial rectus relieves the discomfort.

This study proved that one-step adjustable-suture strabismus surgery under DTFNBA is an effective alternative when patients are properly selected. Because it does not interfere with muscle tone, DTFNBA produces a more accurate result than retrobulbar, peribulbar or sub-Tenon's anaesthesia. Further studies are required to test the usefulness of this technique for vertical, oblique strabismus and to correct diplopia, as these patients were not included in the present study.

We conclude that, when using the appropriate selection criteria and techniques, one-step adjustable-suture strabismus surgery using DTFNBA is an effective alternative to peribulbar block for most young patients requiring strabis-

Table 2 Number of patients with each pain score at various stages of the operation on the medial rectus. Differences between groups were tested using the Mann–Whitney test (*$P<0.05$)

	Group 1 (peribulbar block)			Group 2 (DTFNBA)		
	No pain	Discomfort	Pain	No pain	Discomfort	Pain
Conjunctival incision	50	0	0	50	0	0
Muscle hooking	50	0	0	35	15*	0
Muscle suture	50	0	0	50	0	0
Muscle cutting	50	0	0	50	0	0
Scleral suture	50	0	0	50	0	0
Conjunctival suture	50	0	0	50	0	0

mus surgery. The technique avoids the disadvantages of other types of local and general anaesthesia.

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BJA

CASE REPORTS

Cardiac arrest after administration of Omnipaque radiocontrast medium during endoluminal repair of abdominal aortic aneurysm

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We describe a case of acute cardiovascular collapse in a patient with end-stage renal failure undergoing endoluminal repair of an abdominal aortic aneurysm. The 61-yr-old man suffered cardiac arrest shortly after administration of radiocontrast medium (Omnipaque), during deployment of the endovascular device. He had received the same contrast solution for diagnostic angiography on the previous day. He was successfully resuscitated and recovered completely. The differential diagnosis and management are discussed.

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Endoluminal repair is a new, minimally invasive technique for surgical treatment of abdominal aortic aneurysms,[1] involving transfemoral insertion of an intraluminal prosthetic graft into the infrarenal aorta. Using this technique, the aneurysm sac is excluded from the circulation. The intraluminal prosthesis is anchored to the normal aortic wall above and below the aneurysm using an expandable balloon or self-expandable metallic hooks. The technique requires image intensifier guidance and intra-arterial administration of radiopaque contrast. If used successfully, this method carries the advantages of reductions in morbidity, blood loss, hospital stay and cost.[2] However, vessel rupture and failure of technique can lead to conversion to an open surgical repair. In addition, reactions to radiocontrast media (RCM) contribute a significant morbidity.

Case report

A 61-yr-old male was admitted for endoluminal repair of an abdominal aortic aneurysm (EAAA). A 6 cm infrarenal aortic aneurysm had been diagnosed 4 months previously. His aneurysmal disease was suitable for endovascular graft placement and he was offered the treatment. He had a history of ischaemic heart disease and malignant hypertension with end-stage renal failure. He was on regular haemodialysis using a well-functioning arteriovenous fistula and maintained a good quality of life. His current medication included Imdur, diltiazem, aspirin and erythropoietin. He denied allergy to food or drugs. Preoperative investigations showed: haemoglobin 12.4 g dl^{-1}; platelets 192×10^{9} litre^{-1}; Na^{+} 138 mmol litre^{-1}; K^{+} 5.2 mmol litre^{-1}; urea 13.6 mmol litre^{-1} and creatinine 677 mmol litre^{-1}.

On the day of admission the patient had aortography to define the precise position of the aortic stent; 100 ml contrast solution (Omnipaque) was used.

For the endovascular procedure the next day, anaesthesia was induced with fentanyl 100 µg, propofol 140 mg and atracurium 50 mg, and maintained with isoflurane (inspired concentration 0.8–1.2 vol%) and nitrous oxide in oxygen (nitrous oxide >50%/oxygen >30%). The right radial artery and right internal jugular vein were cannulated for continuous monitoring of arterial pressure and right atrial pressure and the patient was transferred to the operating theatre. Surgery proceeded uneventfully for 2 h There was no administration of additional drugs, colloid or blood during this period. For maintenance therapy, 0.9% sodium chloride 5 ml kg^{-1} h^{-1} was given.

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Immediately before the attachment of the endoluminal stent to the aortic wall, 250 ml radiopaque contrast (Omnipaque) was injected via the right femoral artery to determine that it was positioned correctly. Shortly afterwards, the deployment of the graft with expansion of the balloon was completed.

Five min after administration of the radiocontrast material, the arterial pressure decreased markedly. The systolic arterial pressure decreased progressively and reached 20 mm Hg despite administration of increments of ephedrine (30 mg in total), epinephrine 1 mg and crystalloids 1000 ml. The heart rate was 130 beat min^{-1} but no cardiac output was detected. Indirect cardiac massage was started as electromechanical dissociation arrest was evident on ECG. Arterial blood gases at this time were: pH 7.4, Pa_{CO_2} 4.77 kPa, Pa_{O_2} 24.0 kPa, base excess −1.8 and Sa_{O_2} 99.6% with FI_{O_2} 1.0. No bronchospasm, rash or periorbital oedema were observed.

Resuscitation continued for 20 min and comprised epinephrine 3 mg and norepinephrine 1 mg, four units of blood, crystalloids 2000 ml and colloids 1000 ml.

Within 30 min, the systolic arterial pressure stabilized at 70–80 mm Hg with a continuous infusion of epinephrine 0.1 $\mu g\ kg^{-1}\ min^{-1}$, and the decision not to convert to open surgery was taken. The procedure was completed successfully.

The patient was then admitted to the intensive care unit. An acute systemic reaction to RCM was suspected at that time. Blood was obtained for measurement of serum mast-cell tryptase concentration, routine blood tests and clotting screen. Hydrocortisone 100 mg i.v. was included in the treatment and continuous venovenous haemofiltration started.

The patient's condition improved dramatically over the next few hours, and he was weaned off inotropic support. He was extubated the following morning and was discharged from hospital 4 days later with no side-effects. He was referred to an allergy clinic for further investigations and management.

Three hours after the reaction, the serum mast-cell tryptase concentration was 31.4 ng ml^{-1} (normal range 2–14 ng ml^{-1}). After consultation with the Supraregional Protein Reference Unit based in Sheffield, where the samples were analysed, the true value was estimated to be 60 ng ml^{-1} as a result of the haemodilution effect of the resuscitating fluids. The next two samples, obtained 8 and 12 h after the incident, when the patient was on haemofiltration, showed serum tryptase concentrations of 25.6 ng ml^{-1} and 25.5 ng ml^{-1}, respectively. These results were compatible with mast-cell degranulation. There was also a moderate derangement of the patient's clotting profile: APTT 140 s (control 31.2), PT 23 s (control 12.9) and INR 1.83.

CT scan performed 5 days later showed no leak from the graft, with no free fluid in the retroperitoneal space, favouring the diagnosis of acute anaphylaxis as a cause of the cardiac arrest.

Discussion

Reactions to RCM are well documented.[3] Most case reports concern diagnostic radiological procedures without general anaesthesia. Mild adverse reactions, mostly vasodilatation, occur in 3% of all contrast radiological examinations,[4] but it is the idiosyncratic anaphylactoid reactions that may be fatal and which cause the greatest clinical concern. Few case reports describe systemic anaphylactic reactions mediated via antigen-specific IgE antibodies formed from previous exposure to RCM, but the reactions are thought to have mainly an anaphylactoid character.[5]

There are two groups of RCM: ionic, hyperosmolar (1500 mOsm kg^{-1}) or first-generation solutions, and the newer, second-generation, non-ionic, hypo- and iso-osmolar (350–700 mOsm kg^{-1}) agents. It is widely accepted that the first-generation RCMs are more toxic and more immunogenic and therefore responsible for a higher morbidity, including allergic reactions.

There is emerging evidence,[6] however, that some of the newer non-ionic hypo-osmolar RCMs can trigger a true anaphylactic reaction, directly activating IgE antibodies. Iopamidol and ioversol, for example, have chemical structures that resemble the 'mirror molecules' of succinylcholine and other neuromuscular blocking agents. They have two identical side-chains containing quaternary ammonium groups which can cross-link to IgE molecules. In theory, these new RCM could be more immunogenic than the older first-generation ionic hyperosmolar solutions, but there are insufficient data to confirm this. However, new preparations have significantly lower overall toxicity and fewer side-effects.

In 1970, Ansell reported life-threatening reactions to the first-generation ionic contrast agents in 0.01–0.02% of all radiological examinations[7] but more recently the incidence of a fatal outcome has been reported in only 1 in 40 000 administrations.[8] In 1992, Lieberman reported an incidence of severe, but not necessarily fatal, anaphylactoid reactions in 1–2% of all contrast studies,[9] perhaps attributable to the growing number of radiological investigations and previous under-reporting of adverse reactions. With the introduction of the new generation of non-ionic, low-osmolar RCM, this risk has been reduced 5–10 fold.[4 8]

Iohexol (Omnipaque) is another new, second-generation RCM. It is the most frequently used x-ray contrast medium for arteriography, cardioangiography, urography, hysterosalpingography, gastrointestinal tract and CT investigations. It is a non-ionic, monomeric, tri-iodinated, water-soluble, isotonic solution containing iohexol 140–350 mg ml^{-1}. It is almost 100% excreted unchanged through the kidneys within 24 h of administration. It is less than 2% protein bound and has no detectable metabolites.

Our patient had an acute anaphylactic reaction to contrast medium under general anaesthesia and during a major surgical intervention. The reaction occurred in typical fashion, 3–5 min after administration of the contrast medium and followed re-exposure to the allergen (RCM).[10] The lack of other signs of an acute allergic reaction (e.g. bronchospasm, histamine release) made the recognition of anaphylactic shock very difficult. Furthermore, the time of the reaction coincided with surgical manipulation of the aorta, when aortic rupture is particularly difficult to exclude. Unchanged haemoglobin concentration, lack of abdominal distension and a good response to high doses of epinephrine did not support the diagnosis of vessel rupture. Although we did not suspect an anaphylactic reaction immediately, we ruled out massive blood loss in the operating theatre, and the surgery was completed successfully.

Tryptase is a neutral protease concentrated in the secretory granules of mast cells. It serves as a specific marker for mast-cell activation and its concentration is linearly related to histamine release.[11] We accepted the 5-times-normal-range tryptase concentration as proof of our clinical diagnosis.[12] (Concentrations above 20 ng ml^{-1} are considered indicative of an anaphylactoid or anaphylactic reaction.)

This patient had end-stage renal failure but we followed the renal physicians' recommendation not to haemodialyse before the operation. It is unlikely that haemodialysis before surgery would have influenced the severity of the reaction because the patient was already sensitized to RCM during the previous radiological examination (diagnostic angiography). However, we feel that haemofiltration in the immediate postoperative period contributed considerably to the speed of recovery because of the more rapid elimination of inflammatory mediators.[13]

We believe that this is the first case of anaphylactic shock reported in a patient undergoing EAAA, a technique which is increasingly being used. It is important to draw the attention of anaesthetists to the potential allergenicity of RCM, in particular when contrast solutions are used during surgery. In the case of an acute anaphylactic reaction, prompt recognition and early and continuous treatment remain important for a successful outcome.

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Paradoxical air embolism during hepatic resection

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Systemic venous air embolism is a serious complication in patients with chronic liver disease having liver surgery. Intrapulmonary arteriovenous shunting can permit air emboli to pass into the systemic circulation. We describe a case of paradoxical air embolism detected by trans-oesophageal echocardiography in a patient with cirrhosis who was having a hepatic resection.

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Keywords: liver, resection; embolism, air

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Although the incidence of venous air embolism (VAE) and paradoxical air embolism (PAE) during hepatic resection is unknown, VAE is a potentially harzadous complication during hepatectomy.[1] Many patients who undergo hepatectomy have liver cirrhosis, and VAE is particularly dangerous in such patients because 15–45% have pulmonary abnormalities including intrapulmonary shunting caused by pulmonary vascular dilatation and arteriovenous communication.[2–4] In these patients, paradoxical emboli can occur during air embolism even if intracardiac abnormalities are not present. Transoesophageal echocardiography (TOE) is a most sensitive method to detect VAE[5] and can discriminate intracardiac from transpulmonary passage.[6–8] We report a case of paradoxical embolism after transpulmonary passage of gas detected by TOE in a cirrhotic patient during hepatic resection.

Case report

A male patient (47 yr, 63 kg, ASA II) underwent resection of the right lobe of the liver for hepatoma. He had a 5-yr history of cirrhosis caused by hepatitis B. He had no clinical cardiopulmonary disease and chest x-ray and ECG were normal. The patient was premedicated with midazolam (3 mg i.v.) and glycopyrrolate (0.2 mg i.v.). Anaesthesia was induced with thiopentone and maintained with 1.0–2.0% (inspired concentration) isoflurane and nitrous oxide 50% in oxygen. Muscle relaxation was with vecuronium. Ventilation was mechanically controlled and adjusted to maintain an end-tidal concentration of carbon dioxide ($F\text{E}'_{\text{CO}_2}$) between 3.5 kPa and 4.5 kPa throughout surgery with PEEP of 3 cm H_2O. Arterial blood pressure was monitored invasively from the left radial artery, and oxygen saturation with a pulse oximeter (Sp_{O_2}). Central venous pressure (CVP) was measured intermittently by transducer. After induction of anaesthesia Pa_{O_2} was 277 mm Hg and Pa_{CO_2} 35 mm Hg with $F\text{I}_{\text{O}_2}$ of 0.5. The patient was in the supine postion.

Hepatic resection using electrocautery and ultrasonic dissector was started after clamping the branches of the portal vein and the right hepatic artery supplying the right lobe of the liver.

Two hours and 20 min after the start of operation, an abrupt decrease in $F\text{E}'_{\text{CO}_2}$ (from 32 to 15 mm Hg) and Sp_{O_2} (from 100% to below 60%) were noted. The administration of N_2O was immediately discontinued and the patient's lungs were hyperventilated with 100% oxygen. After a few seconds, systolic arterial pressure decreased from 120 mm Hg to under 20 mm Hg and heart rate fell from 65 beats min^{-1} to less than 20 beats min^{-1} with severe ST depression on ECG monitoring. Embolism was suspected. The infusion tubing was checked, and was found to be satisfasctory. The surgeons acknowledged that a large number of small hepatic veins were cut and open to the atmosphere. The patient's position was changed from supine to left lateral decubitus, and ephedrine 12 mg, atropine 0.4 mg and epinephrine 100 µg given through the central venous catheter. When cardiovascular measurements improved, arterial blood gas analysis showed Pa_{O_2} 161 mm Hg and Pa_{CO_2} 34 mm Hg with $F\text{I}_{\text{O}_2}$ of 1.0. About 5–10 min after the onset of clinical signs,a TOE probe was placed. Air bubbles were seen coming from the right pulmonary vein into the left atrium (Fig. 1). No right-to-left intracardiac shunt was found by colour flow echocardiography. Although the number of air bubbles decreased progressively, they continued to appear in the left heart from the right pulmonary vein for 20 min.

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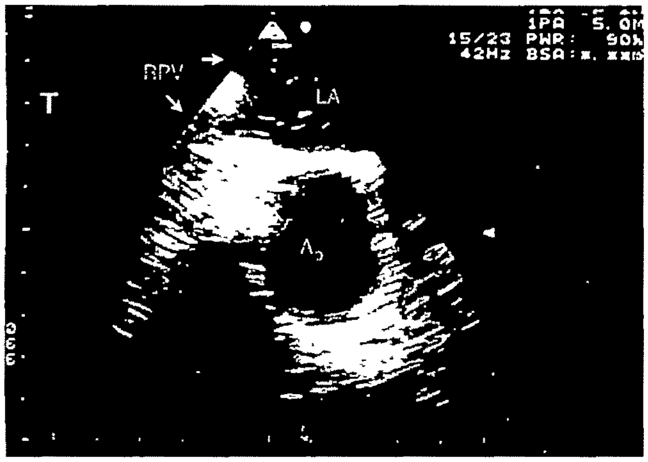

Fig 1 Short-axis view at the level of mid-oesophagus transoesophageal echocardiogram showing the right pulmonary vein (RPV), left atrium (LA), and aorta (AO) About 5 min after the reduction of end-tidal $\mathrm{CO_2}$, air bubbles were seen within the RPV as they entered the LA, indicating a right-to-left pulmonary shunt

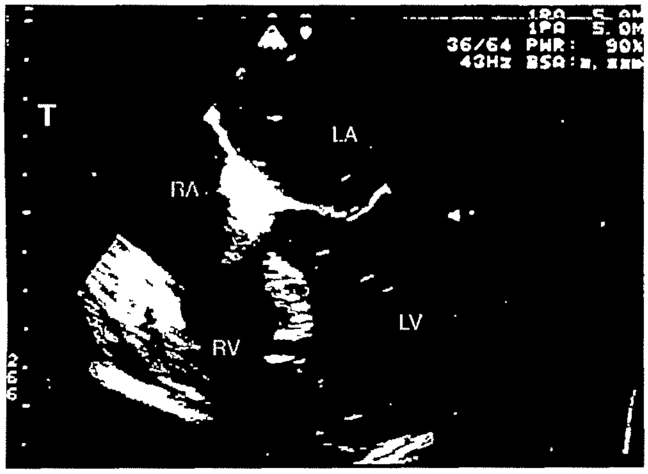

Fig 2 Four-chamber view transoesophageal echocardiogram showing the right atrium (RA), left atrium (LA), right ventricle (RV) and left vebtricle (LV) About 15 min after the reduction of end-tidal $\mathrm{CO_2}$, air bubbles were seen continuously only in the LA and LV There were no air bubbles within the right heart

During this time no air bubbles were seen in the right heart (Fig. 2). These findings suggest that embolism had occurred from cut small hepatic veins being exposed to the air, and passed through dilated pulmonary vessels and appeared in the left heart.

After induction of anaesthesia, CVP was 7 mm Hg. It was not possible to measure CVP continuously during resuscitation period. After return of cardiovascular stability, a pulmonary arterial catheter was inserted, and pulmonary arterial pressure was 21/8 mm Hg and CVP of 6 mm Hg.

Hyperventilation was continued with 100% oxygen. An infusion of low dose dobutamine was given until the air bubbles had disappeared. At the end of surgery (1 h after the reduction of $F\mathrm{E}'_{\mathrm{CO_2}}$), $Pa_{\mathrm{O_2}}$ was 395 mm Hg and $Pa_{\mathrm{CO_2}}$ was 43 mm Hg with $F\mathrm{I}_{\mathrm{O_2}}$ of 1.0 The patient was extubated 3 h later in the intensive care unit, and the early postoperative course in intensive care unit was satisfactory. There was no clinical evidence of pulmonary oedema or neurological sequelae

Discussion

Previous studies have highlighted the potential dangers of VAE during hepatic resection.[1] VAE is particularly worrisome in patients with chronic liver disease who may have intrapulmonary arteriovenous shunting,[2] for air can pass into the systemic circulation (i.e. paradoxical air embolization) without any intracardiac abnormalities. The incidence of VAE and PAE during hepatic resection is unknown.

VAE is unlikely to occur in patients undergoing abdominal procedures while in the supine position, unless the inferior vena cava or pelvic veins are exposed to the air.[9 10] However, during hepatic resection, vena cava manipulation or compression may narrow its diameter at the junction with the hepatic veins. In such a situation, the venous distending pressure of the constricted portion of the inferior vena cava may be less than in the nonconstricted part, and becomes even subatmospheric when blood passes through the narrowed portion with a high flow rate. Air could be sucked into the inferior vena cava *via* the large number of small hepatic veins exposed to the atmosphere.[1] In our case, the inferior vena cava was being compressed while a large number of small hepatic veins were open to the air.

The effects of air embolism depend on the volume as well as the rate of air entry. Adornato *et al.*[11] reported that slow infusion of air (0.01 to 2.00 ml kg^{-1} min^{-1}) passes through the right side of the heart, occludes the pulmonary circulation and causes a progressive increase in CVP, an abrupt increase in pulmonary arterial pressure (PAP) to a plateau and a progressive decrease in peripheral resistance. The reduced resistance may be compensated for by an increase in cardiac output but hypotension can follow when compensation fails. In contrast, injection of a bolus air (25–200 ml; 1–13 ml kg^{-1}) occludes the right side of the heart, increases CVP, decreases PAP, and causes hypotension. Many clinical episodes of VAE result from combinations of slow infusion and also introduction of larger amounts. In our case, CVP and PAP were not measured during resuscitation but we noted S–T depression, shock and brodycardia. This suggests that a large volume was introduced.

Various methods can be used to prevent embolism. An increase in venous pressure by using PEEP might reduce entrainment of air into the circulation or stop air entrainment after air embolism has been detected.[12] This is controversial because an increase in venous pressure might cause paradoxical embolism if the patient had a right-to-left shunt.[13] We used 3 cm H_2O of PEEP and, this was reduced during resuscitation. Another method to prevent VAE is changing position during operation. During the parenchymal phase of the operation, some suggest that the patients should be in a Trendelenburg position of about 15°.[14] In our case, the patient was supine, since we have done about 200 cases of major hepatic resection with this position without previous incident.

When VAE has developed, a position of head-down and left lateral decubitus can protect from embolism effects.[11] In our case, after the reduction of $F\text{E}'_{\text{CO}_2}$, the lateral decubitus position was used because we suspected slow entry of the air.

PAE occurs when the air in the venous system or in the right heart passes through an intracardiac channel and reaches the systemic circulation. A persistent patent foramen ovale exists in 10–35% of the population and is the most common route for PAE.[15] However, air may also reach the systemic circulation through pathological dilatation of intrapulmonary vessels normally present in some people (but more frequent in end-stage liver disease).[16] In the normal individual, pulmonary parenchymal precapillary and capillary blood vessels have a diameter of 8–15 μm.[17] However, in patients with chronic liver diseases, intrapulmonary shunting can occur by intrapulmonary vascular dilatation (up to 160 μm) at the precapillary level, or by direct arteriovenous communications.[17 18] Hopkins *et al.*[3] reported that 47% of cirrhotic patients had right-to-left intrapulmonary shunting, shown by contrast echocardiography. In this case, TOE demonstrated air bubbles passing from the right pulmonary vein into the left atrium. No right-to-left intracardiac shunt could be detected by colour flow echocardiography. These findings suggest that the source of PAE was from dilated pulmonary vasculature and not from an undignosed intracardiac shunt.

TOE and precordial Doppler ultrasound are the most sensitive modality in detecting VAE[5] and can discriminate intracardiac from transpulmonary passage.[6–8] In patients with intracardiac communications, immediate opacification of the left heart chambers occurs after arrival of air into the right heart chambers. However, in patients with transpulmonary passage, air passes into the pulmonary circulation where it is trapped in capillaries with diameter of 8–15 μm. It is either absorbed into alveolar space or dissolved during pulmonary transit, if the size of bubbles are less than 8 μm in diameter.[19] When pulmonary vessels are dilated at the pre-capillary level (>15 μm), delayed opacification in the left atrium occurs approximately three to six ventricular contractions after leaving the right ventricle.[6] In this case, we placed a transoesophageal probe about 5–10 min after the onset of signs and air bubbles were still seen arriving in the left atrium *via* the right pulmonary vein. An intracardiac shunt was not seen. These findings suggest pulmonary vasodilatation.

Intrapulmonary shunting is implicated in the pathophysiology of the hypoxaemia observed in patients with chronic liver disorders.[20] However, three out of five patients with vascular dilatation had Pa_{O_2} values of 82 mm Hg or more while breathing room air.[4] In our case, the patient was not hypoxic before the operation.

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Skin necrosis following injection of non-steroidal anti-inflammatory drug

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We report two patients who developed skin necrosis following an intramuscular injection of non-steroidal anti-inflammatory drug into the anteriolateral area of their thigh. Both patients required further multiple operations and one developed life threatening septicaemia. They were left with disfiguring scars. Skin necrosis, although rare, is a recognized adverse reaction to intramuscular non-steroidal anti-inflammatory injections. It is likely that the injections were, unwittingly, administered subcutaneously. It is important to ensure intra-muscular administration, with an appropriate needle length.

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Non-steroidal anti-inflammatory drugs (NSAID) are frequently prescribed analgesics in the postoperative period. Well-known side effects include gastric or duodenal ulceration, skin rashes, as well as renal and liver toxicity, and bronchospasm, especially in asthmatics.[1 2] Tissue necrosis is recognized as a rare but serious consequence of NSAID injection,[3] potentially leaving the patient with life-long disfigurement. We present two patients who developed this complication.

Case 1

A 35-yr-old man underwent an arthroscopy of his knee under general anaesthesia. For postoperative pain relief he received an i.m. injection of ketoprofen (Oruvail) in the anteriolateral aspect of his thigh whilst under anaesthesia. In the recovery room, he complained of pain and a red rash on his thigh. This was thought, at the time, to be a mild reaction to the drug. He was reassured and discharged home.

The patient was seen 12 days later in outpatients. He explained that the initial erythematous rash had turned a deep purple colour over the initial 24 h and then over the following days had faded. He was now getting more pain from this area than from his knee. On examination the patient looked unwell and was pyrexial. The rash had developed into a necrotic lesion measuring 10×10 cm with a sloughy green surface.

He was admitted to hospital, started on i.v. antibiotics, and he underwent wound debridement with daily dressings until the wound was clean enough to accept a skin graft. Although only a 90% skin graft take was achieved; the remaining raw areas were allowed to heal conservatively, leaving a very obvious indented scar. He also had an area of anaesthesia distal to the site of injury.

Histology of the necrotic tissue showed full dermal necrosis and necrosis of the subcutaneous fat. There was associated focal thrombosis within vessels and a marked acute inflammatory infiltrate.

Case 2

A 33-yr-old, moderately obese woman, underwent arthroscopy of her left knee. In the anaesthetic room diclofenac (Voltarol) was injected into the left upper outer thigh. A tourniquet was applied over this area. The arthroscopy lasted 25 min. Postoperatively the patient complained of intense itching around the injection site, which was noted to have a red discolouration. This area of inflammation subsequently necrosed over the next 2 days.

The wound management was complicated by development of severe cellulitis affecting the whole leg a week after the operation. This responded well to i.v. antibiotics. The wound was gradually desloughed with local dressings over the next month. This created a

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defect measuring 4 cm in diameter and 5 cm in depth. An attempt at delayed primary closure failed because of infection and further dressings were required.

A further attempt at wide local excision and primary closure was undertaken 4 months after her original surgery. This did not heal and a sinus developed with an underlying abscess, which required incision and drainage. Gentamicin beads were inserted into the defect. The patient again developed severe cellulitis and septicaemia that required intensive care support for 2 weeks.

A year after the original operation, the patient still had a large and painful wound on her thigh that required daily packing. The vicious circle of sepsis and wound breakdown was finally stopped by the patient undergoing a wide excision of the soft tissue 10 cm in diameter taken down to the fascia. The wound was skin grafted and it healed without further complications. Histology confirmed wide-spread fat necrosis with chronic inflammatory changes.

The patient was so unhappy with the cosmetic result that she eventually underwent tissue expansion of the surrounding skin, allowing advancement flaps and a linear wound closure.

Discussion

The term Nicolau Syndrome (synonym: embolia cutis medicamentosa) has been coined to describe skin necrosis following i.m. injections.[4 5] Soon after the injection there is pallor of skin around the injection site with associated pain. This is followed by erythema that evolves into a lividoid violaceous patch. The involved area subsequently becomes haemorrhagic and then necroses. Scarring is an inevitable outcome.

The pathogenesis explaining the cause of skin necrosis is uncertain. However, the most common hypothesis is damage to an end artery.[3 5] The other causes to consider, especially with tissue necrosis, are the cytotoxic effect of the drug or the additives in the injectate.

These two cases highlight the potentially serious consequences of tissue necrosis following injections of NSAID. They demonstrate that the area of tissue damage with diminished vascularity often extends beyond the visible area of necrosis. Failure to recognize the extent of fat necrosis and poor tissue perfusion in the wounds leads to inadequate debridement and poor wound healing. They are then prone to repetitive cycles of infection and wound breakdown, resulting in multiple surgical procedures. Both patients were left with extensive scarring, soft tissue indentation and unsightly skin grafts.

Cockshott and colleagues[6] have highlighted the difficulties in administering an intramuscular injection. They showed that there was a variable depth of subcutaneous tissue dependent on the sex and weight of the patient. They demonstrated that only 5% of females and 15% of males would receive a gluteal i.m. injection with a standard 3.5 cm long needle (19 gauge green needle) and that the rest would receive a subcutaneous injection. It is almost certain that these two patients received subcutaneous injections, as clinically and histologically there was no muscle necrosis.

The authors believe that the information given in the advisory sheets accompanying NSAID injections is not explicit enough with respect to this potentially serious complication. For instance, the drug information sheet of ketoprofen warns that pain or a burning sensation may occur around the injection site. It advises that the injection should be given by deep intragluteal injection in the upper outer quadrant of the buttock. If more than one injection is required then alternative sites should be used. This would obviously include the upper outer thigh, which was the site involved in both cases. The potential for subcutaneous injection and consequent subcutaneous tissue necrosis is not mentioned. Only in the more commonly used Voltarol injection is there a warning that there is a rare incidence of local pain and induration and, in isolated cases, you may get abscess and local necrosis.

NSAID are effective analgesic agents and i.m. injections are an accepted means of administration. Unfortunately, there is a relatively high chance that the injection will be administered, unwittingly, into the subcutaneous tissue. Even though subsequent skin and soft tissue necrosis remains a rare complication, it can occur. Specific warnings should be added to the drug information sheet.

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Recurrent neurological symptoms in a patient following repeat combined spinal and epidural anaesthesia

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A healthy woman developed neurological symptoms after two consecutive Caesarean sections under combined spinal and epidural anaesthesia. Amethocaine was used for spinal anaesthesia and mepivacaine for epidural anaesthesia on both occasions, and a combination of fentanyl and bupivacaine was continuously infused for pain relief after the second. Her symptoms on both occasions were similar, including pain in the buttocks of 7–11 days duration and numbness in the sacral area of 5–6 months.

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Keywords: anaesthetic techniques, combined subarachnoid and epidural; complications, neurological; anaesthetics local, amethocaine; anaesthetics local, hyperbaric; anaesthetics local, mepivacaine

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Regional anaesthesia for Caesarean section is generally held to be inherently safe. Spinal and epidural blocks are therefore used widely, with the more recently introduced combined spinal and epidural technique gaining popularity.

Since Schneider and colleagues[1] reported four patients in whom pain in the buttocks or lower extremities developed following recovery from spinal anaesthesia, it has been realized that such symptoms after uncomplicated spinal anaesthesia are not as rare as thought previously. However, the symptoms usually disappear within a week or two, and have been termed transient neurological symptoms (TNS). In addition, despite its name, pain is seldom accompanied by neurological deficits. In contrast, prolonged or persistent neurological symptoms, including cauda equina syndrome, have been associated with continuous spinal anaesthesia[2] or intended epidural anaesthesia,[3] and rarely with uneventful single shot spinal anaesthesia[4] or combined spinal and epidural anaesthesia.[5] Recently, we became aware of a patient who developed pain and persistent hypoaesthesia in the buttocks and legs after two consecutive Caesarean sections under uneventful combined spinal and epidural anaesthesia.

Case report

A 28-yr-old, woman (weight 70 kg, height 154 cm) was admitted at term for elective Caesarean section because of cephalopelvic disproportion. She had neither a remarkable medical history nor abnormal routine laboratory investigation. She was premedicated with atropine 0.5 mg i.m. With the patient in the left lateral decubitus position, combined spinal and epidural anaesthesia was performed using a double-needle, double-interspace method. The lumbar area was cleansed with an iodine-containing solution and wiped dry; then, approximately 3 ml of a 1% lidocaine solution was infiltrated at the L1–2 level and the L3–4 level for epidural anaesthesia and spinal anaesthesia, respectively. Using a sterile technique, an 18-gauge Tuohy needle was placed in the epidural space with the bevel directed cephalad *via* the midline approach using the loss of resistance to saline technique. An epidural catheter (Portex, Kent, UK) was advanced 5 cm into the epidural space, and aspirated to exclude intrathecal or i.v. placement. A 25-gauge Quincke needle was then introduced into the subarachnoid space at the first attempt without difficulty. After aspiration of approximately 0.2 ml of clear cerebrospinal fluid, 2 ml of 0.5% amethocaine in 10% glucose was injected over approximately 15 s. No paresthesias were elicited during needle insertion with either technique, catheter insertion, or intrathecal anaesthetic administration. The patient was then immediately turned to the supine position with left uterine displacement for surgery

Since an upper dermatomal level of block for pinprick discrimination 20 min after the injection was T-10 bilat-

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erally, 10 ml of 1.5% mepivacaine was administered through the epidural catheter to obtain a more cephalad sensory level. The surgical procedure was uneventful and lasted 45 min. An additional 10 ml of 1.5% mepivacaine was administered immediately before the completion of surgery. The anaesthetic level was maintained at T-6 bilaterally and haemodynamic values remained stable throughout the intraoperative period. The epidural catheter was removed in the operating room and the immediate postoperative course was uneventful. Two days after surgery, the patient reported a sacral area of numbness and a moderate burning pain in the buttocks radiating to the dorsolateral sides of both thighs. There were no signs of bladder or bowel dysfunction. A diclofenac sodium suppository was administered to relieve pain. Although the painful sensation resolved within a week, the numbness continued for 5 months.

At age 31 yr, she was again admitted at term for her second Caesarean section because of the previous surgery. Preoperative neurological examination revealed no sensory-motor or muscle-tendon reflex abnormalities. Combined spinal and epidural anaesthesia was again performed using the same method. Intrathecally, 2 ml of 0.5% amethocaine in 10% glucose was injected over approximately 20 s, and a sensory block to pinprick was obtained at T-8 bilaterally. No paresthesias were elicited during the whole procedure. Since she complained of some pain immediately after the start of surgery, 9 ml of 2% mepivacaine was administered through the epidural catheter to obtain an upper sensory level of T-5 bilaterally. No clear fluid was aspirated from the epidural catheter before the injection. The surgical procedure was uneventful and lasted 30 min. An additional 10 ml of 1.5% mepivacaine was administered epidurally, immediately before the completion of surgery, and the continuous epidural infusion of 0.001% fentanyl and 0.2% bupivacaine was started thereafter at a rate of 2 ml h^{-1} for 48 h postoperatively. Haemodynamic values remained stable throughout the intraoperative period.

Although the immediate postoperative course was uneventful, she again complained of numbness in the buttocks 12 h after surgery, when neurological examination revealed no motor disturbance but hypoaesthesia in the S3 dermatomal area. Next day, a tingling pain developed in the buttocks radiating to the dorsal area of the left thigh which became more intense after continuous epidural infusion was stopped. A diclofenac sodium suppository was administered to relieve pain, which lasted 11 days. The patient denied difficulty in voiding or defaecating. The numbness slowly decreased and disappeared 6 months later.

Discussion

We have presented a case of recurrent neurological deficits and pain after combined spinal and epidural anaesthesia. During both procedures, appropriate doses of amethocaine were administered for spinal anaesthesia and mepivacaine was used for epidural anaesthesia. A combination of bupivacaine and fentanyl, the doses of which were also reasonable, was continuously infused through the epidural catheter for postoperative pain relief after the second Caesarean section. Symptoms on both occasions were remarkably similar in nature, degree and duration. The pain was characterized as burning or tingling and lasted only 7 or 11 days, respectively. In contrast, hypoaesthesia in the sacral area was rather persistent, lasting 5 or 6 months.

The characteristics of the pain on both occasions were remarkably similar to those of previous cases of TNS after the administration of a single injection of lidocaine,[1] mepivacaine,[6] amethocaine,[7] and bupivacaine.[8] One common feature of all these cases and the findings of prospective studies[9 10] were moderate-to-severe pain in the buttock, lower back, and/or legs that appeared 1–24 h postoperatively after complete recovery from uneventful spinal anaesthesia. The pain was often characterized as dull, aching, cramping, sharp, or radiating. In most cases, the symptoms resolved fully within 1 or 2 weeks and neurological examination was normal.

Persistent neurological symptoms were initially reported after continuous spinal anaesthesia[2] or intended epidural anaesthesia.[3] Maldistribution, repeated injection, and relatively large doses of local anaesthetics have been implicated. However, Beardsley and colleagues[11] recently described them after uncomplicated spinal anaesthesia. As part of their clinical investigation concerning epidural and spinal anaesthesia, one volunteer developed a minor sensory deficit lasting for 3 months in the sacral area after a slow injection of 2 ml of 5% lidocaine. Subsequently, Gerancher[4] reported cauda equina syndrome, which involved bladder and/or bowel dysfunction, after an uneventful lidocaine spinal. Additionally, Auroy and colleagues[12] performed a prospective multicentre study, in which two out of 40 640 cases incurred permanent sensory deficits. These reports have suggested that even a recommended dose of local anaesthetic can cause neurological injury. Despite no direct evidence, many anaesthetists have proposed that persistent or permanent neurological symptoms are likely to result from a direct toxic effect of local anaesthetics.

In contrast, the aetiology of TNS has been controversial, since neurological deficits have rarely been associated with pain. For example, Freedman and colleagues[9] demonstrated in their recent epidemiological study that 118 out of 1864 patients who had spinal anaesthesia developed TNS and, out of 118, only four patients reported neurological symptoms such as lower extremity weakness, numbness, and/or paraesthesia lasting less than 1 month. We[10] previously showed in our prospective study that only one out of 11 patients who developed TNS after amethocaine spinal anaesthesia had numbness, which lasted for only 3 days.

Although our patient did not incur bladder or bowel dysfunction, the duration of numbness in the sacral area (>5 months) makes the symptoms worthy of note. The similarity in location between pain and hypoaesthesia in our patient suggests that both TNS and neurological injury may share a common mechanism and that TNS may be related to a direct neurotoxic effect of local anaesthetic solutions.

Although the similarity in symptoms on the two occasions suggests that the repeated events may have resulted from the same mechanism, it is not clear which procedure was responsible for the symptoms; spinal anaesthesia, epidural anaesthesia, and/or postoperative epidural analgesia. It has been demonstrated that TNS can follow amethocaine spinal anaesthesia although the incidence is lower compared with lidocaine.[10] In addition, Freedman and colleagues[9] demonstrated in their clinical study that one patient developed TNS accompanied by numbness in the lower extremity after spinal amethocaine. Epidural anaesthesia alone has been associated with TNS,[13] but not persistent neurological symptoms, as long as the catheter is inside the epidural space. In our patient, although the proper positioning of the epidural catheter was not confirmed on both occasions, the catheter was probably kept in the epidural space because there was no aspiration of cerebrospinal fluid and there was a complete and rapid motor recovery after surgery. Another possible explanation involves diffusion of the local anaesthetic from the epidural into the intrathecal space through the dural hole made by the 25-gauge spinal needle. Since a top-up with mepivacaine had to be given twice and once on the first and second occasions, respectively, the cauda equina incurred a relatively large exposure to mepivacaine. Finally, it is possible that postoperative epidural analgesia was responsible for the symptoms. However, the postoperative pain management described has been used in our institution without causing similar neurological symptoms or muscle weakness.[14] Moreover, many other researchers [15–18] have recommended using similar dosage of bupivacaine.

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Loss of the guide wire: mishap or blunder?

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We describe four cases of lost guide wires during central venous catheterization. Although percutaneous catheterization of central veins is a routine technique, it is a procedure requiring advanced operating skills, expert supervision, and attention to detail in order to prevent adverse effects.

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Percutaneous catheterization of central veins is a routine technique. The complication rate of central venous cannulation may be as high as 12%.[1–3] The Seldinger technique, originally used to cannulate vessels for radiographic procedures, is frequently used for central venous cannulation.[4 5] We report four cases of lost guide wires. Each represents a typical scenario.

Case 1

A 63-yr-old female underwent an uncomplicated anterior resection of the rectum. After surgery, an anaesthetist in his first year of training inserted a central venous catheter *via* the right internal jugular vein. He was not familiar with central venous catheterization or the Seldinger technique and was not supervised. When he encountered resistance while advancing the guide wire, he became nervous but continued with the placement of the catheter. No further problems were noted, but the catheter was then accidentally withdrawn. A second cannulation was performed under supervision, with no problems. The catheter tray was not checked for guide wires after either of the procedures. A check chest x ray was reported to show no problems, and postoperative recovery was uneventful. One week later a routine radiograph of the abdomen displayed a guide wire at the right border of the spine (Figs 1 and 2). The frontal and lateral chest x ray confirmed the suspicion. The first chest x ray was not available for comparison. The guide wire was removed easily by exploration of the right internal jugular vein under general anaesthesia.

Case 2

A 62-yr-old male was scheduled for elective major vascular surgery but the start was delayed. A consultant supervised a first-year trainee. Induction of general anaesthesia was straightforward but draping the patient for surgery impeded access to the neck. The surgeon started the procedure before completion of central venous cannulation *via* the right internal jugular vein. The vein was identified easily and cannulation was performed without problems. Both trainee and supervising consultant were distracted from the cannulation procedure when the surgeon started the operation. The consultant anaesthetist concentrated on the management of the anaesthesia while the junior anaesthetist continued with central venous catheter placement. No right atrial ECG could be detected despite sinus rhythm. While flushing the catheter, undue resistance was met, but this caused no suspicion. On the postoperative chest x ray a guide wire was seen extending from the inferior part of the *vena cava* to the right internal jugular vein (Fig. 3). The guide wire was removed using a Dormier basket.

Case 3

A 68-year-old male in septic shock and multiple organ failure after resection of the rectum was receiving intensive care. During a busy night-shift, a fifth-year trainee cannulated the patient's left femoral vein to establish venous access for haemofiltration. Information about another sick patient distracted him from holding on to the

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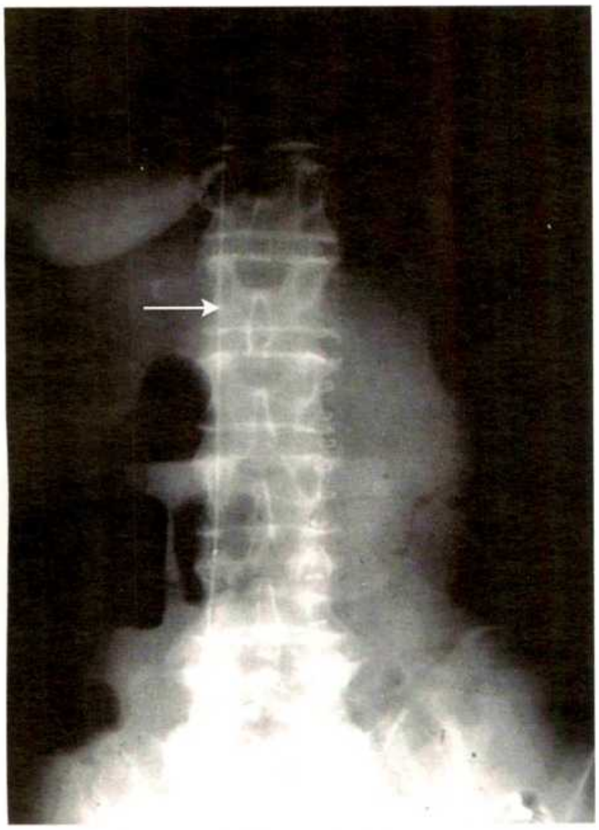

Fig 1 Case 1. Plain abdominal radiograph. Arrow indicating guide wire.

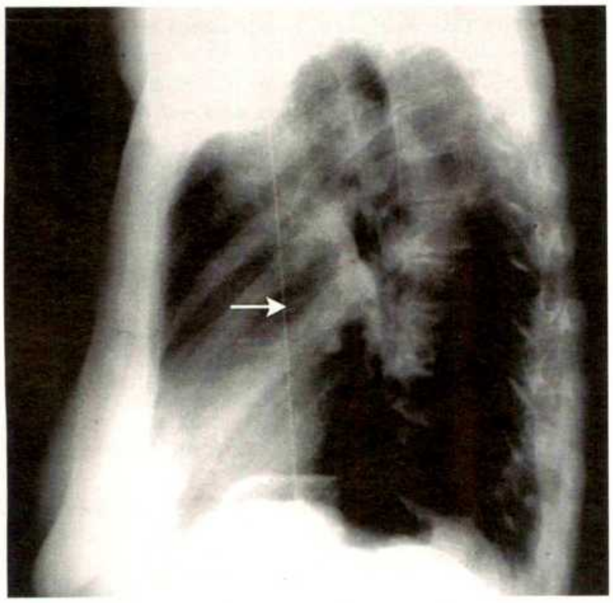

Fig 2 Case 1. Lateral chest x ray. Arrow indicating guide wire.

guide wire. The next morning he remembered no problem with the venous catheterization. On the routine chest x ray the guide wire is clearly visible, but was not reported by the radiologist. A day later, after placement of a multiple lumen catheter *via* the right internal jugular route, the guide wire was noted and removed.

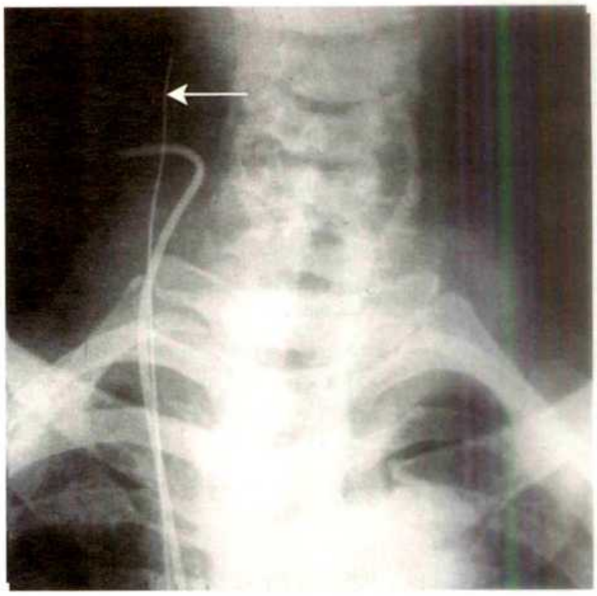

Fig 3 Case 2. chest x ray. Arrow indicating guide wire.

Case 4

An experienced physician passed a cannula into the left jugular vein of a 43-yr-old man with a subarachnoid haemorrhage using the Seldinger technique for the first time. He had been taught the technique, in particular the handling of the guide wire, but carried out the procedure without supervision. No problems with catheterization were recorded. A check chest x ray showed the distal end of the guide wire within the catheter. The guide wire could be held within the catheter by two clamps, and catheter and guide wire were removed together by careful traction.

Discussion

Other complications of central venous cannulation are discussed elsewhere.[6–8] We report the unnoticed intravascular insertion of a complete guide wire. This is a rare and completely avoidable complication of central venous catheterization. The guide wire should be held at the tip at all times to prevent passage into or out of the vessel. If this rule is followed, the guide wire cannot get lost. These four cases show that standard operating procedure may be overlooked. Predisposing factors for an intravascular placement of the guide wire include:

- inattention (all cases);
- inexperienced operator—either in method (i.e. Seldinger technique) or actually central venous cannulation *per se* (Cases 1, 2 and 4);
- inadequate supervision of trainees (Cases 1, 2 and 4);
- overtired staff (Case 3).

The signs of guide wire loss include:

- the guide wire is missing;

- resistance to injection *via* the distal lumen;
- poor venous backflow from the distal lumen;
- guide wire visible on a radiograph.

Consequences of guide wire loss include embolism from fragments of catheters or guide wires which can be fatal in up to 20%,[9] but no data exist on lost guide wires. In contrast to such emboli, the loss of a complete guide wire usually does not cause symptoms. In general, the guide wire is found by chance on a radiograph and has not been missed previously. There are no data on the complications of lost guide wires, but such a foreign body could cause arrhythmias, vascular damage, thrombosis and embolism. Guide wires should be removed as quickly and completely as possible.[10]

Interventional radiology is the method of choice. With modern devices a lost catheter, guide wire fragment, or entire guide wire should be able to be removed in most cases.[11] During the intervention the patient should be heparinized.[12] Usually the foreign body (e.g. the guide wire) is caught by a gooseneck snare passed *via* the femoral vein using radiographic control.[11] The use of endovascular forceps or a Dormier basket increases the risk of endovascular trauma.[12] If the foreign body is captured, it is usually necessary to remove it along with the vascular sheath. If the vascular sheath is twice the size of the lost catheter or the lost guide wire it may be possible to withdraw the foreign body through it.[12] If heparinization is contraindicated, extraction should be attempted by careful surgical exploration.

Each single step of central venous cannulation can cause serious complications. These complications should be understood by the operator and continuous attention during the procedure is vital. With the Seldinger technique, the following precautions should be taken.

- Inspect the wire for defects before insertion.
- Consider a guide wire to be a delicate and fragile instrument.
- When resistance to insertion is met, remove and inspect the wire for damage, reposition the introducer so that no resistance to its passage is felt.
- Particular caution should be used when attempting central catheter placement in patients who are predisposed to thrombosis or have had repeated catheterizations of a particular vessel.
- If multiple manipulations are needed, reinspect the wire and replace it if necessary.
- Pass catheter over wire into the vein.
- Make sure that the wire is visible at the proximal end, before the catheter is advanced.
- The catheter should be 'railroaded' over the guide wire into the vein, holding the wire, and not pushing catheter and wire together into the vein.
- Always inspect the wire for complete removal at the end of the procedure [13].
- Hold onto the wire at all times until removal from the vessel.

Conclusion

Percutaneous central venous puncture is a procedure requiring advanced operating skills, expert supervision, and meticulous attention to detail. To prevent adverse effects we must abandon the practice of 'See one—Do one—Teach one' and must make sure that trainees are aware of all possible complications. The loss of a guide wire is a completely preventable complication provided that one always holds on to the tip of the wire.

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Correspondence

How to avoid fatal complications after central venous catheterization

Editor—Booth and colleagues report a case of fatal cardiac tamponade after the placement of a central venous catheter.[1] We appreciate that Booth and coworkers decided to publish this case as we believe that a great number of serious complications of central venous catheterization remain unpublished. We had to act as expert witnesses in an unpublished case in which the insertion of the same type of single lumen catheter ('Leader Cath', Vygon Ltd., Ecoven, France) also caused cardiac tamponade and circulatory failure, resulting in persistent cerebral damage in an 18-yr-old woman. The catheter had been introduced without electrocardiographic (ECG) guidance and chest X-ray had been done too late.

Why did Booth and colleagues state that the ECG willl not indicate the catheter tip position and that ECG may only be useful when chest x-ray cannot be done immediately? We think that chest x-ray is not routinely warranted as ECG monitoring during central venous catheter placement is an excellent technique that excludes unrecognized malpositioning. This technique was first described more than 50 yr ago.[2] With an intraluminal wire or saline, the tip of the catheter is used as an electrode to obtain the intra-atrial or intraventricular ECG. As the catheter tip enters the right atrium, the P wave amplitude increases until it is almost as tall or greater than the QRS. The catheter is then retracted until the normal P wave is observed. Almost 40 yr ago, neurosurgeons used this technique for the first time to place ventriculo-atrial shunts.[3] Apart from detection of a pneumothorax chest x-ray is unnecessary after placing a central venous catheter with ECG monitoring.[4,6] The ECG guidance technique may, however, be more difficult in patients with arrhythmias. Booth and coworkers did not mention any details of the cardiac rhythm of their patient.

This interesting report raises further questions. The patient already had a triple lumen central venous catheter at the time the single lumen one was placed. The authors did not mention how far the guidewire and, subsequently, the catheter were advanced. It remains unclear why three lumen were insufficient to administer drugs and infusions, and why a fourth lumen was thought to be necessary for parenteral nutrition. What was the rationale for the overhasty transfer of the parenteral nutrition to the new single lumen catheter before an x-ray was obtained?

The authors mention that the carina represents a landmark on chest x-ray as it lies at the upper limit of the pericardial reflection over the lower superior vena cava.[1,8] They state that there is almost no risk of catheter-induced cardiac tamponade using this landmark, but they did not mention the exact position of the first central venous line in relation to the carina.[1] How can the authors exclude that the first catheter may have perforated the pericardium? Why had all the catheters been removed from the patient before autopsy, according to a 'standard procedure'? Did the heart show any pathological changes that predisposed the patient for the complications that occurred?

The report from Booth and colleagues demonstrates that easy aspiration of blood and detection of pressure waveforms measured from the catheter are not sufficient to avoid fatal complications after central venous catheter placement. However, these techniques are commonly used in the operating theatre when chest x-ray is not performed before the central venous line is used. Placing a central venous catheter without fluoroscopic or ECG guidance results in malpositioning in at least 15% of patients,[9] and the incidence of severe complications is unknown.[1] There are numerous prospective trials indicating that endocavitary ECG can accurately predict superior vena cava placement.[7] This method is easy to use, fast and highly cost-effective. To our knowledge, there are no reports of complications after central venous catheter placement under proper endocavitary ECG control. We are convinced that fatal cardiac tamponade and other serious complications can be avoided when central venous catheterization is performed under ECG guidance.

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Editor—Booth, Norton, and Mulvey use their case report[1] and some of the literature available on this topic to make several suggestions regarding what they perceive as inadequacies of current clinical practice. We are of the opinion that there are substantial uncertainties regarding this particular case. It is far from clear, either theoretically or from an evidence base, what benefit radiological or echocardiographic investigation in the operating theatre would offer in terms of reducing morbidity and mortality from central line insertion.

Very little information is given about the central line insertion process and there are several points about this and the later management that would need examining in order to determine if some other factor played a significant role in this tragic event.

(i) What was the experience of the operator and was supervision adequate?

(ii) Why was a pressure trace felt to be necessary after free aspiration of blood? Was there some reason that another confirmatory test was felt necessary? We note that a pressure trace was not obtained immediately following insertion of the first catheter.

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(iii) Despite an initial diagnosis of intra-abdominal haemorrhage, the most appropriate investigations were felt to be a chest x-ray and an echocardiogram.

(iv) The authors have not offered the reader an hypothesis as to how and when catheter perforation occurred (if indeed it did). Without post-mortem evidence of catheter position this is difficult. However, this is precisely the reason that one cannot determine how the problem could have been prevented or detected earlier.

In evaluating the appropriateness of an investigation, sensitivity, specificity, yield, risk and cost need to be considered. It is not clear in this case whether any imaging technique used at a single time point (i.e. at line insertion), would have allowed earlier diagnosis or prevented the fatal outcome. The major limitation of single time point imaging (whether it be plain x-ray, fluoroscopy, ultrasound or echocardiography) is that it will only confirm appropriate line position at that time. The benefits and risks of performing single time point imaging of central lines prior to their use in theatre on large numbers of patients are uncertain.

In conclusion, we believe that the exact pathogenesis of the tamponade in this case is inadequately elucidated. It is inappropriate to suggest major changes to accepted clinical practice on the basis of a small number of heterogeneous case reports, particularly when one considers the number of such lines inserted worldwide without problem. We strongly contest the view of the authors that the use of central venous catheters in operating theatres without prior use of these investigations is negligent.

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1 Booth SA, Norton B, Mulvey DA. Central venous catheterization and fatal cardiac tamponade. *Br J Anaesth* 2001; **87**: 298–302

Editor—The case reported by Booth and colleagues[1] reminds us that malposition of a central venous catheter is associated with potentially lethal complications. In 1989, the FDA recommended that central venous catheters should not be placed, or be allowed to migrate, within the cardiac chambers.[2] Why do these complications still occur? As Booth and colleagues comment, a chest x-ray is necessary to check catheter tip position before the safe use of any central venous catheter Unfortunately, a chest x-ray is mainly done to eliminate the mechanical complications of the catheter insertion (e g pneumothorax) and less frequently to direct repositioning to a correct location (outside the right atrium (RA)).

Recently, we have carried out two cross-sectional studies. The aim of both was to observe the incidence of malpositioned central venous catheters in hospital patients. The first was done in patients admitted to the wards (not ICU) in our hospital. We showed that with up to 50% of central venous catheters, the distal tip was lodged in the RA.[3] The second, multicentre study (seven ICU), revealed that up to 23% of the central venous catheters were malpositioned. The most striking and common finding to both studies was that the catheters had not been repositioned to the correct location once the chest x-ray had been seen. This finding does not seem to be only a local problem. McGee and colleagues,[4] in an American multicentre study, carried out in ICU, verified that in 47% of patients, the catheter tip was intracardiac, and as occurred in our studies, this malposition was not corrected after taking a chest x-ray. A recent multicentre study of malpositioned central venous catheters, surprisingly defined a correctly positioned catheter as the distal tip being within the superior vena cava or RA.[5] Only ignorance of many aspects of the care of patients with central venous catheters can explain the complications reported.[6] We recommend the development of similar studies in other hospitals to determine and to correct, if necessary, the position of central venous catheters and thus to prevent this 'avoidable complication'.[7]

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Editor—We thank the correspondents for entering into the debate over this case. Detail removed from the manuscript during the editorial process, in part necessitates these enquiries.

We feel it important to state that the left-sided catheter was inserted to the highest possible standards by an anaesthetist approaching completion of specialist training. The right-sided catheter had been *in situ* for several days prior to ICU admission and was deemed unsuitable for postoperative parenteral nutrition therapy in accordance with local infection control policy. The waveform from the right-sided catheter was transduced continuously following ICU admission, and the tip position had been checked on two chest x-rays. The central venous pressure data in the case report were obtained from this catheter The appearance of the waveform transduced from a catheter is one method of excluding intra-arterial tip placement. Surgical review of the patient's abdomen excluded a diagnosis of haemorrhage, and chest x-ray and echocardiography were thought to be the next logical steps. We agree that the lack of a further post-insertion x-ray and the post-mortem findings, prevent elucidation of the cause of the tamponade, but this is not unusual.[1] However, the time interval between the start of the parenteral nutrition infusion through the left-sided catheter and the onset of tamponade is significant. Following this case, our local coroner instructed that medical devices be left *in situ* until post-mortem examination.

The methods utilized in checking the left-sided catheter did not prevent a fatal complication, yet they are commonly relied upon in the operating theatre. Isaac and Dwenger point out that this is accepted practice, but is it good practice? Silva highlights the high incidence of malpositioned catheters in some studies, although this should be reduced by use of catheters 15 cm in length. Intraoperative tamponade may occur only infrequently, but there is a significant ongoing perioperative risk of it in current UK practice. By analogy, a small incidence of tragic events in the dental chair and from hypoxic gas mixture has led to a change in standards.

We agree with Raymondos and Panning that use of the described ECG method would enhance safety. However, Raymandos and Panning do not say if they have sufficient confidence in the ECG technique to start a high flow rate infusion without an x-ray. Our case illustrates the rapidity with which tamponade may occur if a catheter is misplaced even if only low volumes of fluid are used. We have emphasized the need for ongoing vigilance when using a central venous catheter, precisely because no single time point test is foolproof.

The argument that testing of the catheter followed accepted clinical practice, was unsuccessful in the medicolegal defence of this case. We cannot see the logic for a different outcome if the line had been placed perioperatively and used before x-ray. A retrospective analysis of dialysis catheter placement indicates that x-ray before use is unnecessary,[2] but we do not believe that a prospective study of this thesis would receive ethical approval. Whilst we do not advocate the practice of defensive medicine, we feel that the realities of the current medicolegal climate warrant a re-evaluation of current standards of catheter insertion.

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1 Collier PE, Goodman GB. Cardiac tamponade caused by central venous catheter perforation of the heart: A preventable complication. *J Am Coll Surg* 1995, **181**: 459–63
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Is it safe to artificially ventilate paralysed patients through a laryngeal mask?

Editor—We read the editorial by Sideras and Hunter[1] with interest and wish to make the following comments. The single-use LMA† (LMA-Unique™) is made entirely of medical grade PVC[2] and is silicone-free. The study of 11 910 patients[3] referred to in the editorial was prospective and not retrospective as stated by the authors.

Regurgitation into the oesophagus and aspiration of gastric contents. Bernardini and colleagues[4] studied the incidence of complications associated with LMA usage in 15 229 patients undergoing elective surgery with general anaesthesia, including 349 patients weighing more than 100 kg, 684 undergoing major abdominal surgery, and 249 for laparoscopic procedures. Ninety-four per cent (n>14 300) received intermittent positive pressure ventilation (IPPV) with the LMA. Six cases of regurgitation (0.04%), two of laryngospasm (0.01%) and one case of aspiration (0.006%) occurred. The latter patient made a full recovery within 24 h. The authors state that aspiration 'should not have occurred with more appropriate anaesthetic management'. The study concludes that complications with LMA use were similar to those found with tracheal tube usage. The incidence of non-fatal aspiration, despite IPPV being utilized in more than 14 300 patients, is lower than the 1 in 11 910 or 0.008% reported by Verghese and Brimacombe.[3] A meta-analysis in 1995[5] suggested a higher incidence of three aspirations per 12 901 or 0.02% Bernardini's work adds to the large, published body of evidence available on the safety and efficacy of LMA use in fasted adults and children.[6–9]

The three isolated case reports of non-fatal pulmonary aspiration of gastric contents cited in the editorial refer to patients breathing spontaneously through the LMA—they were not receiving IPPV. The editorial also refers to studies involving small groups of patients breathing spontaneously through the LMA with a high incidence of mid-oesophageal but without clinical evidence of aspiration.[10] The editorial does not explain why others using the same methods, including the use of neuromuscular blocking drugs and IPPV in patients in the supine,[11] and lithotomy position,[12] were not able to reproduce these findings. It is, therefore, difficult to interpret the clinical significance of mid-oesophageal regurgitation as it does not appear to be a consistent finding, and, when detected, its presence does not indicate a risk of pulmonary aspiration. Neuromuscular blockade is not required for insertion of the LMA or for instituting and maintaining IPPV. It is required only to facilitate surgical access or to optimize conditions for tracheal intubation through the LMA or the ILMA. The authors do not offer any hard evidence to support their contention that the use of neuromuscular blocking drugs and IPPV with the LMA results in an increased incidence of pulmonary aspiration.

Although intended for use in fasted patients, the LMA with IPPV has been successfully used in non-fasted patients as a rescue device during cardiopulmonary resuscitation[13,14] and, in the 'cannot-intubate-cannot-ventilate' scenario in a wide variety of surgical procedures,[7] including emergency Caesarean sections, without incident.[15] The UK and European Resuscitation Committees, The American Heart Association and American Society of Anesthesiology have endorsed its use in both these situations respectively. The successful use of the LMA in these situations without aspiration of gastric contents despite the use of IPPV and neuromuscular blocking drugs, deserve comment and have not been addressed in the editorial.

The routine use of tracheal intubation is not without attendant morbidity and mortality. Cohen and colleagues[16] reported 101 aspirations in 112 721 anaesthetics, giving an incidence of 0.09% (1 in 1116) Olsson and colleagues[17] reported 87 aspirations in 185 385 general anaesthetics or 0.05% (1 in 2131), with a morbidity of 1 in 3944 and a mortality of 1 in 45 454 general anaesthetics.[17] Warner and collleagues[18] cite an incidence of 67 aspirations in 215 488 anaesthetics—15 occurred during 13 427 emergency operations (0.11%) and 52 in 202 061 patients undergoing elective surgery (0.025%). Also reported was a morbidity of 1 in 16 576 (0.006%) with a mortality of 1 in 71 829 general anaesthetics (0.0013%).[18] It would appear that the incidence of pulmonary aspiration of gastric contents consequent on LMA use, including the use of IPPV, is similar to that encountered with a tracheal tube in fasted patients. Importantly, there are no reports of fatal pulmonary aspiration of gastric contents consequent to LMA use, including its use with IPPV.

Huxley and colleagues[19] suggest that asymptomatic aspiration of gastric contents may occur during sleep in 45% of normal individuals and in up to 70% of patients with depressed consciousness.[19] The 'gold standard' for isolating the trachea from the contents of the gastrointestinal tract in both fasted and non-fasted patients is the tracheal tube. It is, however, only effective in preventing aspiration if successful insertion and inflation of a suitable tracheal cuff occurs before aspiration It is well recognized that a number of aspirations occur both before and during attempts at tracheal intubation, as well as after removal of the tracheal tube. Tracheal cuff design also plays a significant role in preventing gastric contents gaining access to the lungs.[20,21] High volume low-pressure tracheal cuffs, in intubated patients in the intensive care unit, allow methylene blue dye leaks through their longitudinal folds and into the trachea [22,23]

Tracheal intubation is not without attendant morbidity, and adverse outcomes associated with respiratory events constitute the largest class of injury in the ASA Closed Claims Study.[24] Inadequate ventilation, oesophageal intubation, and difficult tracheal intubation account for 75% of these adverse respiratory events. Airway trauma comprises 6% of anaesthesia malpractice claims and occurs mainly in outpatients and females. Laryngeal injuries include those resulting in vocal cord paralysis, granuloma formation and arytenoids cartilage dislocation, which may even occur during short-term intubation.[25] The risk: benefit ratios in fasted patients appear to favour the LMA, with its minimal invasiveness and the lower incidence of iatrogenic short and minimal long-term morbidity.

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Gastric insufflation. Gastric insufflation may occur during IPPV with a LMA only if the tip of the LMA is incorrectly positioned (i.e. not at the upper oesophageal sphincter), and excessive inflation pressures are used. Clinical detection of sub-optimal placement of the LMA is not reliable. Du Plessis and colleagues[26] showed that the commonly used indicators of 'ease of spontaneous breathing' and ease of assisted ventilation and IPPV through the LMA were found to be clinically acceptable in 139/139 patients, but fibreoptic laryngoscopy through the LMA tube showed that 19/139 masks were inadequately positioned.[26] Using fibreoptic laryngoscopy, the vocal cords and arytenoids are visualized in more than 90% of patients following LMA insertion with the recommended technique A view of the oesophagus or upper oesophageal sphincter indicates incomplete or incorrect LMA insertion and is difficult to detect clinically.[12] The tip of the cuff of a correctly placed LMA forms a loose plug over the upper oesophageal sphincter, and Fullekrug and colleagues[27] deliberately withdrew the LMA tip from the sphincter, under direct fibreoptic control, to study its opening pressures.[27] In cadaver studies, the LMA attenuates liquid flow between the oesophagus and pharynx,[28] and this mechanism may help to explain the low incidence of aspiration. Use of excessive inflation pressures during IPPV with a correctly inserted LMA should cause an audible leak and spillage of gases to the atmosphere *via* the oral cavity rather than to the stomach.

The LMA-Proseal™, the newest variant of the LMA, improves laryngeal seal permitting the safe use of higher inflation pressures without leakage. The oesophageal vent or drainage tube serves to separate the respiratory and gastrointgestinal tracts, provides access to gastric contents, and facilitates clinical confirmation of correct positioning without fibreoptic laryngoscopic verification.[29]

Based on calculations of international sales figures (personal communication, LMA International services, Henley on Thames, UK), there have been over 100 million uses of the LMA over the past decade without fatality. Applying the method for calculating the incidence of aspiration used in the editorial,[1] LMA usage should have resulted in at least 9000 incidents of aspiration and 400 deaths. It is unlikely that this level of morbidity and mortality could occur without comment.

In conclusion, the authors do not offer any direct evidence to support their opinion that the jury was still out regarding the use of IPPV with the LMA. The LMA is a major advance in airway management and anaesthesia and no longer merits being treated with suspicion.

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[††] Conflict of Interest Dr Verghese is in receipt of an annual honorarium from LMA International SA.

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Primary pulmonary hypertension in pregnancy

Editor—We read with interest the case report of Monnery and colleagues,[1] describing the fatal clinical course of a pregnant woman presenting with primary pulmonary hypertension (PPH). This case report again emphasizes the point that pregnancy complicated by severe pulmonary hypertension is usually fatal. Women with PPH should be advised against pregnancy. While we agree with the operative management of this patient, we disagree with the medical care after surgery. This patient had severe pulmonary hypertension, with a systolic pulmonary artery pressure of 100 mm Hg, and was doing well on iloprost and epoprostenol (Prostaglandin I_2). For unknown reasons, i.v. epoprostenol therapy was replaced by nifedipine on the fifth postoperative day. Her clinical course was then complicated by recurrent syncope and increasing signs of right heart failure resulting in readmission to intensive care. Although i.v. epoprostenol therapy was re-introduced, her clinical condition deteriorated further leading to her death.

A recent case report describing a similar case of pregnancy and pulmonary hypertension showed a much more favourable maternal-fetal outcome with epoprostenol therapy continued post-partum.[2] Based on earlier reports, we believe for two reasons that epoprostenol therapy should have been continued in this patient and not replaced by nifedipine. First, a combination vasodilator with a calcium-channel blocker may have been useful in this patient, but changing a successful therapy to a therapy with unknown effect with the added risk of severe systemic hypotension and death is not justified. Second, Riccardi and colleagues showed that echocardiographic variables such as left ventricular septal bowing are highly predictive of nifedipine-induced hypotension and syncope.[3] Although the echocardiographic variables are not described in detail in the case report, the severity of the pulmonary hypertension and the dilatation of the right ventricle suggest that nifedipine should have been avoided in this patient. For these reasons, we believe that replacement of epoprostenol therapy with nifedipine is not appropriate in patients with severe pulmonary hypertension doing well on epoprostenol, without additional clinical tests.

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1 Monnery l, Nanson J, Carlton G. Primary pulmonary hypertension in pregnancy: a role for novel vasodilators *Br J Anaesth* 2001; **87**: 295–8

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Editor—We would like to thank Vonk Noordegraaf and Roeleveld for their comments on our case report of primary pulmonary hypertension complicating pregnancy.

To clarify the postoperative course, we would like to emphasize that 5 days after Caesarean section the patient was haemodynamically stable with relatively low pulmonary artery pressures. Although effective, the dose of epoprostenol was limited by unpleasant side effects. Although no vasodilator trial was performed pre-partum, the weaning of epoprostenol and introduction of oral nifedipine were gradual and undertaken with a pulmonary artery flotation catheter *in situ*. Starting oral calcium channel blockade was not associated with rebound increases in pulmonary artery pressure or pulmonary vascular resistance. Given her wish to nurse her newborn and the requirement for consideration for cardiac transplatation that she be independent at home, it was preferable to maintain the patient on oral calcium antagonists if tolerated. She remained stable for several days on oral therapy before developing syncope and increasing signs of right heart failure, at which time epoprostenol was re-introduced.

Our patient underwent Caesarean section before either of the articles referred to by Vonk Noordegraaf and Roeleveld were published. At that time, there was some evidence that long-term epoprostenol conferred benefits over conventional treatment in non-pregnant patients with primary pulmonary hypertension.[1] However, there was little consistency in the way in which the epoprostenol infusions were administered. Had that data been available at the time, given that our patient did have echocardiographic variables suggestive of a poor outcome with nifedipine, it is likely that we would have persevered with the epoprostenol for longer.

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[1]*Dorchester*
[2]*Dundee*
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1 Higenbottom T, Butt A, McMahon A, Westerbeck R, Sharples L. Long-term intravenous prostacyclin (epoprostenol or iloprost) for treatment of severe pulmonary hypertension. *Heart* 1998; **80**: 151-5

Remember the straight laryngoscope

Editor—In his review of 'Recent advances in airway technology' in the *British Journal of Anaesthesia CEPD Reviews*, Gabbott[1] described many devices, but did not discuss the straight laryngoscope. He stated that the McCoy is the most clinically effective new laryngoscope design of the last few years, and also suggested that the reason that other new laryngoscopes have not become popular may be due to lack of good scientific evidence of their usefulness. We would take issue with both these points.

There is no doubt that the McCoy laryngoscope can improve the view of the larynx in relation to the Macintosh laryngoscope, and we support its use. It performs well in studies of simulated difficult intubation caused by restricted head and neck movement. However, in clinical practice it allows visualization of the larynx in less than 50% of grade 3 or 4[2] laryngoscopies.[3–5] There is an explanation for the discrepancy in its efficacy in these two situations.[6]

Only a slight change in the view should be expected with the McCoy laryngoscope, as the basic mechanism of indirect elevation of the epiglottis is identical to the Macintosh blade. This technique is only possible if the tip of the laryngoscope can be positioned in the vallecula, close to the hyoid. An anterior lifting force then advances the hyoid, tensions the hyoepiglottic ligament, and elevates the epiglottis indirectly. Radiological studies show that in difficult intubation patients, some of the tongue remains trapped between the tip of the laryngoscope and the hyoid,[7] and it is not possible to insert the tip into the vallecula. In contrast, it is a reasonable hypothesis that passage of a narrow straight laryngoscope lateral to the tongue and posterior to the epiglottis can allow direct elevation of the epiglottis and visualization of the larynx in these patients. In addition, a successful line of sight of the larynx is more likely with a straight than a curved laryngoscope.[8] Precise technique with the straight laryngoscope is crucial, and uses a lateral approach (the paraglossal or retromolar technique, originally described by Magill[9]). This optimizes control of the soft tissues and further improves the line of sight.[10]

There is much clinical evidence of the efficacy of straight laryngoscopes in difficult intubation patients. A clinical report and review summarized six published series of successful tracheal intubation under vision with the straight laryngoscope, in patients in whom the Macintosh laryngoscope had failed.[10] In a recent report of 29 grade 3 and 4 views with the Macintosh laryngoscope, there was an 89% success rate with the angulated straight laryngoscope, in comparison with 21% with the McCoy laryngoscope[11] (the publisher's error in the figures was corrected later[12]). Within 2 yr of the introduction of straight laryngoscopes to the Western Infirmary, Glasgow, 44% of consultant anaesthetists had managed to achieve a view of the larynx with a straight laryngoscope in patients in whom this had proved impossible with the Macintosh laryngoscope.[13]

We believe that the value of straight, in relation to Macintosh, laryngoscopy is well established, and the technique should now be regarded as a core skill. Certainly, any evidence-based review of airway management is incomplete without discussion of the straight laryngoscope.

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C. M Frerk
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Editor—Thank you for the opportunity to reply to Henderson and Frerk's letter. I accept entirely their point regarding the usefulness of the straight blade laryngoscope. Indeed, I have found the device to be valuable on a number of occasions. I was in two minds whether to mention it in my article but my remit, as I understood it, was to discuss recent advances in relation to 'new' airway devices. The straight blade laryngoscope is not a new device (it was designed before I was born); it is simply becoming popular once again. In retrospect I should have mentioned it, however, and I apologize for its omission. I still stand by my statement that many of the 'new' laryngoscope designs have not been scientifically validated and that the McCoy in particular, is of great value in many clinical circumstances, for example trauma.

D A. Gabbott
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Use of magnesium to treat tetanus

Editor—I read with interest the comprehensive review of tetanus by Cook and colleagues.[1] Experience with treating tetanus and, in particular, the use of magnesium is limited in the UK. There were only 80 cases of tetanus reported to the Public Health Laboratory Service between 1989 and 1999. The published reports on the subject disagree with regard to both requirements for ventilation and on to the effectiveness of magnesium in treating autonomic instability.[2–4] I thought that it would be more informative, given the small number of publications on the subject, to share our recent experience of using magnesium in a patient with tetanus.

A 58-yr-old man was admitted to the ITU with a clinical diagnosis of tetanus. Three days previously he had undergone amputation of toes from his right foot and drainage of an associated abscess. Two days postoperatively he noticed difficulty with mouth opening which worsened over the next 24 h. When the generalized muscle spasms appeared, a diagnosis of tetanus was made and he was transferred to the ITU. When he arrived he had severe trismus and dysphagia, being unable to talk or swallow his saliva. He was having regular muscle spasms and opisthotonus, but not so severe as to interfere with respiration. He had a respiratory rate of 25 bpm, sinus tachycardia (120 beats min^{-1}) and an arterial pressure of 140/95 mm Hg.

Review of his past medical history showed that he was a longstanding insulin-dependent diabetic, and was suffering from peripheral vascular disease. He had previously undergone angioplasty to his right superficial femoral artery, right femoral popliteal bypass grafting, and amputation of other toes from his right foot.

Following his arrival in the ITU, his airway was secured by percutaneous tracheostomy inserted under local anaesthetic. Central venous and arterial lines were inserted. A magnesium infusion was commenced as described by Attygalle and Rodrigo[2] (5 g loading dose, 1–3 g h^{-1}). The patient was treated with metronidazole and i.v. immunoglobulin.

The magnesium infusion controlled most of his muscle spasms within an hour. Occasional breakthrough spasms still occurred, associated particularly with stimulation and movement. The man remained on the magnesium infusion for 22 days While initially he required plasma levels in the range of 3–4 mmol litre^{-1} to control the muscle spasms, after 2 weeks his requirements were reduced, serum levels 2–3 mmol litre^{-1} being more typical. The patient was monitored at the bedside by use of the patellar reflex. This allowed rapid titration of the infusion to take place. Twice daily laboratory assays of magnesium levels were also performed.

The patient's respiratory function remained adequate after commencing the magnesium infusion He did require supplemental oxygen ($F_{I_{O_2}}$ 0.4) to maintain arterial oxygen saturations over 90%, but he remained stable until day 3. Then the patient's gas exchange deteriorated, increased secretions were noted and radiographic appearances of consolidation were found. The patient required respiratory support for the next 21 days, with pressure support ventilation, followed by continuous positive airway pressure only. During this time a number of organisms were isolated from sputum culture, notably coliforms, *Escherichia coli* and *Candida albicans*, which were treated according to sensitivities.

Autonomic instability was not marked in this patient. There were periods of tachycardia and increased bronchial secretions but these events could be explained by other causes. No marked swings in blood pressure or episodes of bradycardia were noted.

The patient was enterally fed *via* nasogastric tube. He required analgesia with morphine for painful experiences such as breakthrough muscle spasms, physiotherapy and change of dressings. Benzodiazepines were used to provide night sedation Tetanus toxoid was given during the patient's stay.

The patient was discharged from ITU after 27 days. His tracheostomy was removed prior to discharge After a further 10 days on the ward, his foot had improved such that he could be managed at home. During this time, the speech therapist continued to review him until satisfactory bulbar function returned. He was discharged from hospital with outpatient follow-up.

Our experience in finding magnesium useful to control spasms without requiring ventilation was similar to Attygalle and Rodrigo.[2] The patient did require ventilation when superadded infection complicated management. I would still, however, agree with the points made by James.[3] If patients with tetanus are managed with magnesium, they should be cared for in an area capable of providing advanced respiratory support.

This patient developed minimal signs of autonomic instability. It is difficult to know if the magnesium suppressed it or if the patient had a less severe form of the disease. The classification provided by Ablett[5] shows that our patient had features of moderately to severe disease. We would, therefore, have expected to see such symptoms. It seems reasonable to conclude that the magnesium was helpful in controlling the instability.

While spasm control could have been provided by deep sedation, it is unlikely that respiratory effort would have been preserved. Considerable atrophy of respiratory muscles would be expected with such an approach. After 20 days of such ventilation it is likely that weaning would have been prolonged. With the use of magnesium, a tracheostomy, and pressure support ventilation, patients are better able to tolerate prolonged respiratory support with requirement for sedation.

Magnesium may not be a satisfactory treatment for all patients affected by tetanus and experience remains limited. It shows considerable promise as a first line treatment for muscle spasm and autonomic instability however, avoiding the need for deep sedation and muscle relaxation.

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UK

1 Cook TM, Protheroe RT, Handel JM. Tetanus: a review of the literature. *Br J Anaesth* 2001; **87**: 477–87

2 Attygalle D, Rodrigo N. Magnesium sulphate for control of spasms in severe tetanus Can we avoid sedation and artificial ventilation? *Anaesthesia* 1997; **52**: 956–62

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5 Albett JJL Analysis and main experience in 82 patients treated in the Leeds Tetanus Unit. In. Ellis M, ed. *Symposium on Tetanus in Great Britain*. Boston Spa, UK. National Lending Library, 1967; 1–10

Editor—We are delighted by Dr Williams' interest in our review. He records a case of the management of moderately severe tetanus with i.v magnesium. The patient was initially managed with spontaneous ventilation but subsequently progressed to supported ventilation.

Magnesium appeared to control the patient's spasm without compromising ventilation but within 48 h he developed pneumonia and required ventilatory support, which lasted for 3 weeks. Tetanus is a disease of muscle rigidity and spasm but with a background of neuromuscular weakness and this must be remembered when considering the use of drugs such as magnesium with muscle-weakening effects[1] The patient did not experience marked autonomic instability and Williams suggests that the magnesium infusion might have prevented autonomic dysfunction from developing. We believe that this is speculation.

There are, indeed, few reports of the use of magnesium in the management of tetanus and only one from the UK The only reports of the use of magnesium in tetanus, like so much of the tetanus literature, are uncontrolled series or case reports. We are, therefore, left with the opinions of informed individuals[2 3] Unfortunately, it is debatable whether anecdotal reports add useful evidence to the debate on the treatment of severe tetanus.

There are good pharmacological reasons to believe that magnesium may be a useful drug in the treatment of severe and very severe tetanus (Ablett class III and IV). What is needed is a randomized controlled trial of adequate size and quality to determine whether the use of magnesium may save the lives of patients who might otherwise die. It is hoped that such a trial will take place in Asia within the next 3 years.

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J M. Handel
Bath
UK

1 Mellanby J, Green J. How does tetanus toxin work? *Neuroscience* 1981, **6**: 281–300

2 James MFM. Magnesium sulphate for the control of spasms in severe tetanus. *Anaesthesia* 1998; **53**: 605–6

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Myasthenia gravis unmasked by neuromuscular blockade

Editor—The case report[1] of undiagnosed myasthenia gravis unmasked by neuromuscular blockade reminded me of a case I had 20 yr ago in the early days of laparoscopy. Unfortunately, I have failed to track down the case notes for detailed reference. The patient was a fit young woman having a diagnostic laparoscopy for chronic abdominal pain My gynaecological colleague used minimal volumes of carbon dioxide (rarely more than 1 litre) for insufflation, so the anaesthetic technique was usually thiopental, nitrous oxide, oxygen and halothane, face mask and spontaneous respiration. Sometimes (as in this case) a small dose of gallamine was added, of the order 30–40 mg—far from a paralyzing dose. My patient's respiration became markedly inadequate, and I assisted it for the approximate 10 min of the procedure. A test-dose of edrophonium produced some improvement and neostigmine caused sustained adequacy of respiration without the use of intubation or a ventilator. Nerve stimulators were not available.

Suspecting that I might have uncovered a subclinical case of myasthenia gravis, I referred the young woman to my physician colleague, but his tests and those of a neurologist were unconvincing. However, in subsequent months, she showed signs of drooping eyelids when tired and eventually went on to oral treatment with pyridostigmine, with significant improvement in her welfare and energy. My suspicion had been ultimately confirmed.

R. A Bowie
Kirkcaldy
UK

1 Dunsire MF, Clarke SE, Stedman JJ. Undiagnosed myasthenia gravis unmasked by neuromuscular blockade. *Br J Anaesth* 2001; **86**: 727–30

Editor—Thank you for the opportunity to reply to the letter from Dr Bowie describing a similar case to that described in our case report.[1] We congratulate him on diagnosing myasthenia in what was a very subtle presentation.

He described a fit, healthy young woman who developed very mild ocular symptoms: Grade 1 myasthenia according to Osserman and Genkins classification.[2] This accounts for only 15% of all myasthenics and commonly presents in women in their second and third decades.[3] The cardinal features of the disease are weakness and increased fatigability of voluntary muscles, due to a reduction in the number of acetylcholine receptors to one third of normal. During laparoscopy, the raised intra-abdominal pressure increases the work of the diaphragm and respiratory muscles, making them prone to fatigue if the patient is breathing spontaneously. Myasthenics are exquisitely sensitive to neuromuscular blocking agents and the combination of respiratory muscle fatigue and a very small dose of relaxant was enough to render respiration inadequate.

It would have been interesting to know what investigations were undertaken by the neurologist in this patient to ascertain the diagnosis. However, it is not surprising that the results were 'unconvincing', as the current standard investigations have a low specificity or yield a high degree of false negatives,[4] in this subgroup of myasthenics. Ultimately, it can become a clinical diagnosis with symptomatic improvement on giving an anticholinesterase, as was illustrated in this case.

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S G. Clarke
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1 Dunsire MF, Clarke SG, Stedmon JJ. Undiagnosed myasthenia gravis unmasked by neuromuscular blockade. *Br J Anaesth* 2001; **86**: 727–30
2 Osserman KE, Genkins. Studies on myasthenia gravis. Review of a twenty year experience in over 1200 patients. *M Sinai J M* 1971; **38**: 497–537
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Potentially dangerous labeling of levobupivacaine

Editor—Due to the national shortage of 0.5% bupivacaine, we have recently started using levobupivacaine (Chirocaine) in our obstetric practice. We were surprised to read the phrase 'for parenteral use only' on both ampoule and packaging of this product (Fig. 1). Although the definition of parenteral is 'by any route other than the gastrointestinal tract', a brief survery of 10 anaesthetists in our department confirmed our suspicions that the term is primarily associated with the i.v. route. As inadvertent i.v. administration of levobupivacaine could have disastrous consequences, we feel that this labeling is misleading and potentially dangerous. We have made our concerns known to Abbott Laboratories Ltd. who have kindly agreed to review this instruction.

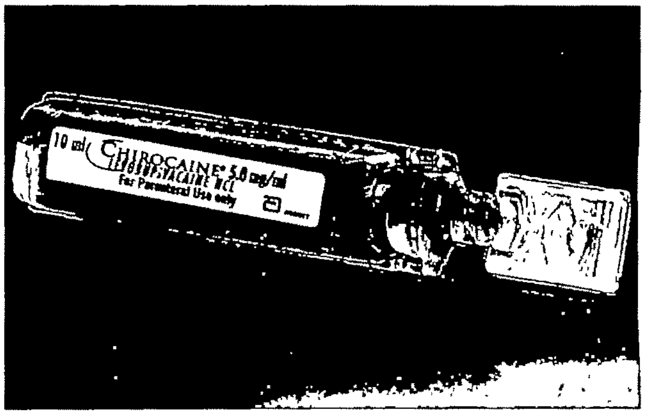

Fig 1 Ampoule of levobupivacaine.

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D. Walker
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1 *Stedman's Medical Dictionary*, 26th Edn. London: Williams and Wilkins, 1995

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Book Reviews

Textbook of Anaesthesia, 4th Edn. A. R. Aitkenhead, D. J Rowbotham and G. Smith (editors). Published by Churchill Livingstone, Edinburgh. Pp. 806; indexed; illustrated. Price £54.95. ISBN 0443063818.

In all honesty, does any reviewer—having been given a deadline by the Journal's Editor-in-Chief—truly look forward to the time-consuming, 'semi-voluntary' task of reviewing a 800 page long textbook of anaesthesia—yet another one—particularly when noticing, after browsing through the list of contents, that the first chapter deals with one's favourite subject: statistics . . . ? But you cannot really skip the very first chapter of a book that you are about to review, can you? I am glad that I started from scratch—not *although* but *because* it started with the chapter on statistics. It is an example for the rest of the text, how even 'tedious' and complex matters can be presented in a highly lucid and readable fashion. If the reader should still fail in understanding some subtleties of statistics, she/he is free to follow the author's advice: 'Readers who cannot see intuitively that this is so are likely to have some difficulties with the mathematical aspects of anaesthesia and should seek help to improve their understanding' (p. 6). (At this point, I seriously asked myself whether I belong to those 'who can intuitively see that this is so', or to those who 'should seek help'. . .)

Having gone through the first chapter, any possible attitude of merely 'having to' quickly turned into one of 'pleasure' to review the fourth edition of the *Textbook of Anaesthesia*. Publication of a fourth edition within 16 yr of the first edition in 1985 is *per se* an indication of its popularity and success. This new edition has been expanded, carefully revised and updated. It is divided into two main sections: *Principles of Anaesthesia* and *Practice of Anaesthesia*. Nineteen new chapters have been added (mostly to the basic science section), including chapters on statistics, cellular physiology and pharmacology, and on the cardiovascular, nervous, gastrointestinal and renal systems. Despite this significant expansion, compared to the previous edition the number of pages has remained almost unchanged, a reflection of tight editorial control. Approximately one third of the chapters of the *Practice of Anaesthesia* section has been written by authors who had not contributed to the third edition in 1996. This improves the presentation of up-to-date information on the continuously changing clinical practice of anaesthesia.

Overall, the quality of the contributions is high. The style is uniform throughout. Each section concludes with a list of five to 10 references (often other textbooks, monographs, review articles, national guidelines) under the heading *'Further Reading'*. The large number of (mostly excellent) tables, figures and diagrams greatly helps in the understanding of more complex subjects. Obviously, in a text for trainees such as this one, chapters on major anaesthetic subspecialties (for example, on cardiac, paediatric and regional anaesthesia, on pain management and intensive care medicine) cannot (and are not intended to) serve as reference text, but only as a brief introduction to the topic.

One measure of success is whether the editors have met their stated goal The stated objectives of the fourth edition of this *Textbook of Anaesthesia* are 'to provide a readable, comprehensive, and concise text to satisfy the needs of new recruits into anaesthesia during the first two years of training and also present this clinical discipline as an integrated development from basic science'. Overall, the editors have clearly achieved their intended goal with great success. The text provides an excellent primer not only for candidates studying for Part 1 FRCA examination but also for the European Diploma of Anaesthesiology.

It does not actually need mention that with the many topics covered, there will be some aspects of content or style which will not satisfy every individual's expectation. At times, my choice of 'representative' references would have been different. Values for minimum alveolar concentration (MAC) are not specified according to age, resulting in the listing of different MAC values in different tables (Tables 3.3 and 13.1). Contrary to accepted opinion, hypocapnia is listed as one of the factors that decrease MAC (p. 152). A paragraph titled 'CO_2 narcosis' (p. 166) does not actually address this issue. 'Locus coeruleus' is misspelled a couple of times as 'caeruleus' (p. 196). Although there has not been any evidence during the past decade of any relevance for coronary steal in clinical practice, the phenomenon is still being discussed in the context of isoflurane (pp. 158–9). Despite the (correct) statement that 'clinically significant liver damage seems theoretically impossible' (p. 159), hepatotoxicity is listed under the heading of sevoflurane in Table 13.2 (p. 163). Perhaps more importantly, the major changes in the International Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care (*Circulation* 2000; **102** [Suppl. I]) have not been incorporated (i.e. automatic external defibrillation now being considered part of basic life support; vasopressin being the vasoactive drug of choice over epinephrine in adult cardiac arrest, and amiodarone being the antiarrhythmic drug of choice over lidocaine in aiding electrical defibrillation and preventing occurrence of ventricular fibrillation).

However, these are rather minor criticisms which do not really distract from the overall value of this publication For the goal stated by the editors, I can recommend the *Textbook of Anaesthesia* without hesitation. Despite a price increase of almost 40% since the last edition only 5 yr ago, it still represents reasonable value for money.

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International Anesthesiology Clinics. Vol. 39: Number 2: 2001 *Xenon*. T. Goto (editor). Published by Lippincott, Williams and Wilkins, Philadelphia, Pp. 107; indexed; illustrated. Price US$83. ISSN 0020 5907.

It is more than 50 yr since the first use of xenon as an anaesthetic in man was reported. That it remains on the sidelines must be suspect, given its apparently attractive pharmacological profile The editor of this volume is unashamedly enthusiastic about the potential for xenon and has commissioned contributions which, although rather repetitive, give the reader a comprehensive understanding of xenon's pharmacology. But it is a moot point whether studying the contributions would allow the reader to come to an unbiased view of the potential for xenon to contribute usefully to their own anaesthetic practice.

That earnest pessimist, Aldous Huxley, wrote in his *Collected Essays* 'From their own experience or from the recorded experience of others, men learn only what their passions and prejudices allow them to learn'. I wonder if, within this observation, we have a clue as to why an anaesthetic with so many splendid properties is not in routine clinical use anywhere in the world. I prefer to believe that I have few passions or prejudices, but let me tell you about my own experience. In common with others, it appeared to me a few years ago that it was

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probably the cost of xenon that had prevented its wider use. The price of xenon was coming down and that of newer agents, such as sevoflurane, was going up, so might not now be the time for a re-appraisal? And so, after ethical approval and with the invaluable support of the British Oxygen Company, our group set about a standard kinetic and dynamic study in volunteers. Now I do not wish to boast, but I have done a lot of this in the past, so I have a fair grasp of what to do and how to do it. Armed with this fair grasp, we were quite unable to produce stable anaesthesia in a single volunteer using inhalational induction with xenon. Afterwards, all the volunteers were nauseated or sick, sometimes for prolonged periods. After discussion with the ethics committee, the trial was abandoned. And here we might have it: negative result studies tend not to go reported and hence the literature is inherently biased in a favourable manner. To be fair, I did find one reference to another group's negative experience in this volume (Petersen-Felix S *et al.*, *Br J Anaesth* 1998; **81**: 742–5), but that was all. So, as a whole, it seems to me that this book suffers from being somewhat optimistic and uncritical. This is a shame, because most of the individual contributions are very useful.

Various groups from Europe describe their clinical experience with xenon in one chapter, as does the editor in another. One of the properties of xenon of interest is that it is inert, which has implications for its toxic potential and environmental effects. The latter is discussed within the context of environmental pollution from more traditional agents by that enthusiastic group from the University at Ulm, whilst effects on the heart and respiration are carefully reviewed by Japanese contributors. There is a review of the electrophysiological effects of xenon, and a useful discussion of how it might produce anaesthesia, by the editor and his colleagues The single contribution from the UK is a nice summary of the pharmacology of xenon by Talat Aziz from Edinburgh. Finally, although the cost is less prohibitive in relative terms than it used to be, it remains significant and as such there is plenty of scope for studies relating to closed circuits and the like. This topic is well reviewed by workers from Europe as well as Japan.

In summary, the individual contributions in this volume combine to give a comprehensive, if somewhat optimistic, view of the use of xenon as an anaesthetic. I leave it to the reader of the whole text and not just this review to conclude whether the contributors also prove Aldous Huxley correct in his little aphorism.

R M. Jones
Southampton

CD Review. TEE on CD: An Interactive Resource. S. N Konstadt and N. C. Nanda (editors). Published by Lippincott, Williams and Wilkins, Philadelphia. Price US$225. ISBN 0-7817-2629-8.

The ability to reproduce video in a teaching resource combined with the ability to jump from image to image, makes the CD-ROM format far superior to the printed page for understanding transoesophageal echocardiography. Lippincott, Williams and Wilkins (LWW) offer 'two for the price of one' by bringing together the *Atlas of Transesophageal (sic) Echocardiography* (N. C. Nanda, ed) and *Clinical Transesophageal Echocardiography* (Y Oka and S. N. Konstadt, eds.) on a disk suitable for PC- or Macintosh-based systems. Viewing the program requires a computer that is minimal by today's 'entry-level' standards; there should be no problem running the disk on machines up to 3 yr old. Installation is quick and straightforward, although the author did have problems upgrading the version of the QuickTime™ player supplied on the disk.

The packaging claims that there are 60 videos in all, including 30 min of narrated video, and over 800 pages of text with 2539 still images. The multiple-choice questions test the knowledge imparted on the disk to the full. Unlike some of its competitors, most of the storage space on the CD-ROM is taken up by using file formats common to both PC and Mac, no space is wasted by having separate sections for each.

Unfortunately, this disk is disappointing. Most of us know how easy it is to 'surf' the internet through the programming language, HTML. Today, we are used to jumping from subject to subject and from text illustrations with ease. Unfortunately, all LWW have done is to transfer the books onto the screen and have failed to use the full extent of the interactive media. There are no links from Nanda's text to the illustrations, and turning from figure to figure is clumsy. It would have been easier to flick through the pages of the book. The figures are viewed in a 'pop-up' window which must be closed in order to move on to the next; this makes using the media a hindrance rather than an advantage. Oka and Konstadt's volume is better cross-referenced, although the pop-up windows persist. The screen area for the text is small and unadjustable. The editors have chosen to keep the two volumes separate so that they sit in apposition to each other rather than being complementary. Overall, the format is cumbersome, staid and looks as if it was made in the mid-1990s rather than at the turn of a new century. It was also disappointing that some of the links to the pictures and references failed to appear and that the videos were kept in an entirely separate section rather than used to complement the text.

However, the content is good. The text is concise and covers most eventualities that the non-specialist cardiologist and cardiothoracic anaesthetist will encounter. It goes without saying that the coverage of basic views, and valvular and ventricular assessment is comprehensive. Similarly, coverage of post-surgical complications (one of the main working uses of TEE) is excellent. The CD-ROM offers little information on congenital heart disease, paediatrics, or the growing speciality of grown-up congenital heart disease but, in its defence, the wide variation in the appearance of those lesions would make an encyclopaedia of that magnitude a life-time's work.

The media is in its infancy (or at least adolescence) Publishers are transferring current texts to electronic format, but there is a gap in the market for a textbook written especially for the medium. Unfortunately, this one is not it. However, the disk compares favourably with the combined costs of the paper version. According to LWW's own website, the books retail at a combined cost of $310, compared with the disk at $225.

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Evidence-Based Pharmacy. Phil Whiffen. Published by Radcliffe Medical Press, Abingdon. Pp 182; indexed. Price £19.95. ISBN 1.85775-384-4.

This book, which comprises 10 chapters, covers a variety of areas including taking pharmacy into the 21st century; evidence-based practice; asking the right questions, the tools of evidence-based medicine; accessing the information; getting the evidence into practice; and managing and generating knowledge. This wide approach takes the reader through each step involved in attaining evidence-based medicine relating to pharmacy

The book is useful reading for all pharmacists in hospital, the community, and the pharmaceutical industry, and also for pharmacy students and other health care professionals who require a useful introduction to evidence-based medicine. Included in the book is a basic introduction, describing the need for evidence-based medicine and the tools used in this area. The author is a pharmacist so the examples and text are all relevant to pharmacy. The reader is guided towards determination of the right evidence and how to assess its value and quality. The book also includes information on the Internet and how to make the best use of it in evidence-based medicine. The range of uses of evidence in pharmacy is shown and specific examples illustrate key points.

The appendices give information on website addresses, journals and other publications from the Department of Essential Drugs and Medicine Policy.

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British Journal of Anaesthesia BJA

Extended Guide to Contributors*

This is a revised version of the Extended Guide to Contributors which appeared in the Journal in 1990. It should be read in conjunction with the formal Guide to Contributors (in all issues of the Journal). It is intended to advise contributors on the preparation of manuscripts, particularly those who are preparing manuscripts for the first time.

The purpose of the *British Journal of Anaesthesia* is the publication of original work in all branches of anaesthesia, including the application of basic sciences. One issue each year deals mainly with material of postgraduate educational value.

Papers for publication and all editorial communications should be addressed to: Professor J. M. Hunter, Editor-in-Chief, *British Journal of Anaesthesia*, University Department of Anaesthesia, Royal Liverpool University Hospital, The Duncan Building, Daulby Street, Liverpool L69 3GA, UK. Tel./Fax: +44 (0) 151 706 4005. Email: bja@liv.ac.uk

Aims of the Journal

The *British Journal of Anaesthesia* publishes original work in all branches of anaesthesia, including the application of basic sciences. In addition, the journal publishes review articles, case reports and reports of new equipment.

Some reasons for difficulty

There are several principal reasons for rejection of papers:

(1) *Poor experimental design or inadequate investigation* (or both). Detailed guidance on this aspect is beyond the scope of the present document but inadequate sample size and/or insufficient power are common faults.

(2) *Bad presentation.* This results from inexperience in writing scientific or clinical reports. Various manifestations of the problem may be combined in one manuscript. These include:

(a) Failure to conform to the accepted layout of a scientific paper.

(b) Failure to distinguish between jargon and technical terminology (see appendix).

(c) Excessive verbosity. Most manuscripts may be reduced by at least 30% with advantage.

(d) Unsatisfactory or confusing presentation of data in tables or figures.

(3) *Poor English style and syntax.* Although journals are not sympathetic to this problem in papers from the English-speaking countries, *British Journal of Anaesthesia* has a long tradition of helping authors from other countries. Inevitably, however, the provision of this help causes delay.

(4) *Insufficient material.* Try not to break down studies into the smallest publishable units.

Guidance for the early stages

Before beginning to write, analyse your objectives carefully.

What is the question which you have tried to answer?

What message is to be conveyed?

Do the data and your interpretation of them justify the message?

It is recommended that guidance is obtained from colleagues experienced in research and in writing scientific manuscripts.

Statistical analysis is usually an essential component of the process of assessing the validity and implications of any results presented in a paper. Initial statistical advice should be sought before, rather than after, the data have been collected. Do not use 'recipes' for statistical analysis which you do not understand. Do not use the methods of the professional statistician unless you have a reasonable understanding of what they mean.

Do not assume that *figures* that have been prepared for audiovisual presentation will be suitable for publication in a journal; the dimensions are nearly always unsuitable for the printed page (see below).

Consult recent issues of the *British Journal of Anaesthesia* and try to find a paper which conforms, in general format, to the paper you plan to write.

Please make sure that the *legal considerations* which are noted in the formal Guide to Contributors have been fulfilled. It is important to remember also that the internationally agreed code on the ethics of human experimentation (Helsinki Declaration) should be adhered to. A breach of this code will result in automatic rejection. *It is essential to state that local Institutional Ethics Committee approval and informed patient consent have been obtained, where appropriate.* When studies have been conducted in animals, it is essential to indicate the appropriate Home Office Licence number in the United Kingdom or note that approval has been granted by local Animal Research Committees in other countries.

Submission of manuscripts

British Journal of Anaesthesia participates in a uniform requirement agreement on submission of manuscripts

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*Copies of this Extended Guide may be obtained from the Editor-in-Chief's Office

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(International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to Biomedical Journals. *BMJ* 1988; **296:** 401-405).

Manuscripts must be accompanied by a covering letter signed by all the authors. This should include: (a) Information on prior or duplicate publication or submission elsewhere of *any part* of the work. Please note that it is unethical to submit the same complete work to two journals simultaneously; a clear rejection by an editor is required before submission to a second journal should be considered; (b) a statement of financial or other relationships that might lead to conflict of interests; (c) a statement that the manuscript has been read and approved by all authors; (d) the name, address, telephone number, fax number and email address, if applicable, of the corresponding author who is responsible for communicating with the other authors about revisions and final proofs.

Four copies of each manuscript (including revised texts unless instructed otherwise by an editor) should be submitted and should indicate the title of the paper, the name(s), full address(es) of the author(s), and be in letter quality heavy type (not dot matrix), double-spaced on one side only of the paper, with a wide margin. Please do not staple the manuscript but use a paper clip. Contributors should retain a copy in order to check proofs and in case of loss. Manuscripts should only be submitted on disk when an editor requests it. Our preferred format is a 3.5″ PC floppy disk with the file written in Word 6 for Windows. However, it is also possible to process disks submitted in other formats, provided sufficient information is supplied to enable conversion to the preferred format. Articles on disk should be prepared in the simplest possible form. Please do not use endnotes, footnotes, etc. for references. Correct fonts, type sizes, column measures, etc, will be added by the technical editor.

Each of the four copies submitted must be accompanied by a complete set of figures. At least one set of figures must be unmounted glossy prints (see below); the other three sets may be photocopies. Annotate photographs as necessary.

The typical layout of the manuscript is:

Title page
Summary, including Keywords
Introduction (not headed)
Methods
Results
Discussion
Acknowledgements
List of references
Tables (including legends to tables)
Legends to illustrations

The pages should be numbered in the top right-hand corner, the title page being page *one*, etc. Start each section on a separate page. For a Short Communication see below.

Title page

A separate page which includes the *title* of the paper. Titles should provide a reasonable indication of the contents of the paper. Avoid enigmatic or vague titles such a 'A new method of scavenging'. Titles in the form of a question, such as 'Is halothane teratogenic?', are often acceptable.

The title page should include the name(s) and address(es) of all author(s). It should be made clear which address refers to which author. An author's present address, differing from that at which the work was carried out, or special instructions concerning the address for correspondence, should be given as a footnote on the title page and referenced at the appropriate place in the author list by superscript numbers (^{1} ^{2} ^{3} etc.) If the address to which proofs should be sent is not that of the first author, clear instructions should be given in a covering note, not on the title page.

A short running title containing not more than 50 characters (including spaces) should be included.

Summary

This should appear on the second sheet and should be presented in fewer than 250 words. It should be structured into four headings: Background; Methods; Results; and Conclusions for all original articles (Clinical Investigations, Laboratory Investigations, and Short Communications) but not for Reviews, Case Reports, or Commentaries. In many respects the summary is the most important part of the paper because it must give the broad objectives of the enquiry, the principal findings and the essential conclusions. Although the reasons for the investigations may be stated, do not give an extensive review. Give the methods of study, in outline only, together with the principal positive findings and any important negative findings. The main numerical data and probability values should be presented concisely. List the main conclusions, but do not discuss the conclusions and more complex issues. Statements such as 'the significance of these results is discussed' are unhelpful. Only in exceptional circumstances is it appropriate to cite references. Abbreviations, other than the standard abbreviations (see below), should appear in the summary only *after* the term has been defined, and only if the term is to be repeated in the summary. In such circumstances, the term should be given once again in full in the text of the paper, with the abbreviation (in parentheses) following.

Keywords

Three to five keywords should be included on the summary page under the heading Keywords. The system used by the journal follows closely that devised by Greene (see *Key Words in Anesthesiology*, ed. Greene NM, 3rd Edn. Amsterdam: Elsevier, 1988).

Introduction

The introduction should give a *concise* account of the background of the problem and the object of the investigation. It should clearly state the aims of the study. Previous work should be quoted only if it has direct bearing on the present problem. For example, a description and evaluation of a system for scavenging anaesthetic gases from an operating theatre need not include an account of the previous literature of the problems of operating theatre contamination by anaesthetic gases and the many studies of morbidity, etc. which may or may not be associated with such contamination. As a rule, the introduction to a paper should not require more than about 200 words.

If a preliminary account of the results has been given in a published abstract, it is customary to refer to this.

Methods

The title of this section may be 'methods', 'materials and methods' or 'patients and methods'. Under no circumstances should the terms 'patients' and 'materials' be regarded as interchangeable. While brevity is essential, the methods must be described in sufficient detail to allow the experiment to be interpreted, and repeated if necessary, by the reader. Previously documented standard methods need not be recounted in detail, but appropriate reference to the original should be cited. Sometimes detailed laboratory techniques may be filed separately in a recognized library and a note to this effect given in the manuscript. Where measurements are made, an indication of the error of the method in the hands of the author should be given. The name of the manufacturer of instruments used for measurement should be given with an appropriate catalogue number or instrument identification (e.g. Radiometer PHM 7). When a manufacturer is unlikely to be known to readers of the journal, the address should be provided also. In the case of solutions for laboratory use, the methods of preparation and precise concentration should be stated.

Drugs. When a drug is first mentioned, it should be given by the international non-proprietary name, followed by the chemical formula in parentheses if the structure is not well known, and (if relevant) by the proprietary name (with an initial capital letter). A figure giving the molecular configuration of the drug is necessary only in the case of the earliest reports of a new drug. The author should indicate in an accompanying note to the editor the source from which he has obtained the molecular configuration; it is an important requirement that the author should check the accuracy of the configuration in every detail. Drug dosages are normally given by the name of the drug followed by the dose (e.g. diazepam 0.1 mg kg^{-1}). Do not confuse drug dose with concentration.

Where the programme of research is complex such as might occur in a cardiovascular study in animals, it may be preferable to provide a table or figure to illustrate the plan of the experiment, thus avoiding a lengthy explanation.

Patients. Data on the mean age (range), weight, sex, height, criteria for selection, etc. should be presented, with an indication of the general state of health and type of operation being undertaken. Animal data on sex, strain and weight should be included. Although it is usually possible to make such a statement in a short paragraph, more complex information may be preferable as a table. However, tables and figures are expensive to produce and should not be used unnecessarily. Where it has been necessary to seek permission from the patients for the type of study being undertaken, this should be indicated.

Anaesthesia. Descriptions of methods of anaesthesia are often unnecessarily cumbersome. The following model is presented as an example of economy of words:

The patients were premedicated with either morphine 10 mg and atropine 0.6 mg (group A) or diazepam 10 mg (group B), both given 1 h before operation. Anaesthesia was induced with thiopental [give rate of injection where appropriate], in a dose sufficient to abolish the eyelash reflex. Succinylcholine 80 mg was given to facilitate orotracheal intubation with a cuffed tube. Anaesthesia was maintained with halothane 0.5–1.0% and nitrous oxide 60% in oxygen, the patient breathing spontaneously from a Magill system. A similar description should be used for animal anaesthesia.

Statistical analysis. Statistical methods must be described with enough detail to enable a knowledgeable reader with access to the original data to verify the report and results. Where possible, findings should be quantified and presented with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Confidence intervals provide a more informative way to deal with a significance test than a simple *P* value. If appropriate a power analysis should be performed before starting the study to determine the number of subjects which need to be studied in each group to detect a given change.

Additional guidance on statistics may be obtained from Guidelines for Statistical Reporting in Articles for Medical Journals (Bailar JC, Mosteller F. *Annals of Internal Medicine* 1988; **108:** 266–273).

Results

Description of experimental results should be concise. Data should not be repeated unnecessarily in text, tables and figures, and unwarranted numbers of digits should be avoided. It is not usually necessary to provide all the data from a complex study: only those values which are essential to the communication should be given. However, results should be presented in a manner so that the reader can check the statistical inferences. If the data are so numerous that this is not possible, the editor must be sent a full set with the submission of the original manuscript and the readers should be informed as to where they can obtain a similar full set of results. The editor has the right to request sighting of the original data collected. As a rule, the following general approach should be adopted:

(1) Prepare all the data in the form of tables.
(2) Decide which data are to be presented in the communication.
(3) Can the essential data be presented succinctly in the text? If not, the essential tables or simplified tables should be prepared.

Tables are important communications and should be accompanied by a legend which makes the table self-explanatory. However, the legend must not contain experimental details, which should be given in the methods section.

Graphs and histograms based on the results should be considered only in the following circumstances:

(1) where a figure will present the data more clearly than is possible in a table.
(2) when an important trend or comparison has to be made for which a graphic presentation is clearly superior to a table or text.

For more detailed guidance on the format of presentation of results, the reader is referred to previous issues of the journal. A common example, however, occurs in the case of a comparison of the findings in two groups of patients who have been treated with different drug regimens. The following example that required revision is based on a submitted manuscript, with the permission of the authors:

> *First draft*
>
> There were 43 patients in the pethidine group and 41 in the morphine group. Table 2 shows that the two drug groups were evenly matched in terms of age, weight and duration of operation.
>
> Sixty to ninety minutes after the injection, there was a reduction of anxiety score of 2.9 points in the pethidine group (highly significant $P < 0.001$) and a reduction of 1.3 points in the morphine group (significant $P < 0.01$). The difference in the magnitude of the reduction of anxiety between the two groups was not statistically significant. Both groups showed a further significant reduction to normal in the anxiety rating when tested again 24 hours after the operation.
>
> Twenty-four hours post-operatively each patient was asked if she recalled seeing any picture cards before the operation. Only 12 out of 43 pethidine patients (28%) could remember all three pictures, while 27 out of 40 morphine patients (68%) were able to recall all three picture cards (Table 3). This indicates a significantly greater incidence of amnesia with pethidine than with morphine ($P < 0.01$) using this test. This persisted for 24 hours in three pethidine and five morphine patients.
>
> Local erythema was present in twelve pethidine patients and in ten morphine patients ninety minutes after injection. This disappeared in the pethidine patients but was still present in the ten morphine patients twenty-four hours after surgery ($P < 0.01$).

> *Second version*
>
> Forty-three patients received pethidine and 41 received morphine. The groups were similar in age, weight and duration of operation (Table 2). Sixty to 90 min after injection there was a mean reduction in the anxiety score of 2.9 after pethidine ($P < 0.001$) and 1.3 after morphine ($P < 0.01$). The difference between the two groups was not significant. Both groups showed a further significant reduction to the normal range when tested 24 h after the operation.
>
> Twenty-four hours after operation each patient was asked if she recalled seeing any picture cards before operation. Only 12 of 43 in the pethidine group (28%) could recall all three pictures, compared with 27 of 40 in the morphine group (68%) ($P < 0.01$) (Table 3). This persisted for 24 h in three patients in the pethidine group and five in the morphine group. Ninety minutes after injection, local erythema was present in 12 of the pethidine group and 10 of the morphine group. This was still present 24 h after surgery only in the 10 who had received morphine.

In the results section there should be no attempt at a discussion of the findings.

Discussion

This requires discipline by the writer for two reasons: first, they may feel that the task is nearly completed and that they are subject to fewer constraints; second, many authors seem to wish to read into their data more than is actually there. The form of a discussion should normally follow this pattern:

(1) Summary of the major findings.
(2) Qualifying remarks in relation to these findings; for example, mention any important uncertainties in the methods of measurement. In laboratory studies, try to relate the concentrations used to those encountered clinically.
(3) Succinct comparison of the present data and relevant data from previous studies.
(4) Deductions—which may explain important differences between the data of the present study and the data of previous studies.
(5) Conclusions from the present study. The original contribution to knowledge from the present study is stated.
(6) The implications of the conclusions for anaesthetic practice and the indications for further enquiry in this area of interest.

Authors should remember at all times, but especially in writing the discussion, that they will spoil their manuscript by excessive length. A discussion of more than three pages is often too long.

Acknowledgements

It is inappropriate to acknowledge routine assistance from nursing or surgical colleagues without which any form of clinical research would not be possible. It is essential to acknowledge all sources of financial assistance and any conflicts of interest.

References

Except for review articles, long lists of references are usually inappropriate. Restrict references to those that have direct bearing on the work described and cite only references to books and articles published in *Index Medicus* and *Index Veterinarius* journals.

References must be numbered consecutively in the order in which they are first mentioned in the text, with the exception of review articles, when references should be arranged alphabetically in the reference list and numbered accordingly in both list and text.

References in text, tables and legend should be identified by Arabic numbers appearing in the text in superscript, for example ^{5} or $^{5\text{–}7}$ or ^{5}<space>^{16} for unrelated references. When a table or figure is first mentioned, its reference must continue the sequence.

Papers which carry a different system of reference will be returned to the authors for re-typing. The scope for major printer's errors in attempting to rectify inappropriate schemes is considerable.

References in the text. If it is considered essential to cite names of the authors of a study in the text (in addition to the identifying number), up to three names should be cited (A; B and C; D, E and F). In the case of four or more authors, 'G and colleagues', 'G and co-workers', 'G and others' are acceptable. The expression '*et al.*' is not used in the text.

An informal reference to previous work (Z's study or Y's study) is permissible only in a paragraph which contains the reference cited formally.

Abstracts that are more than three years old should not be used as references.

Text references to 'unpublished observations' or 'personal communications' should not be included in the final list of references. Personal communications should be cited in the text as (Brown AB, personal communication, year). Authors are responsible for verifying that the wording of references to unpublished work is approved by the persons concerned. This should be provided in writing with the first submission of the manuscript.

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There should be a *table of references* at the conclusion of the paper, commencing on a new sheet. It should be prepared as follows. The names and initials of more than six authors and/or editors should be abbreviated to three names followed by *et al.*

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Names and initials of six authors (if more than six, list three followed by *et al.*), title of paper, abbreviated title of journal, year of publication, volume number, first and any change in last page numbers:

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Monographs.
Name of author and initials, title of book (italics), number of edition, town of origin, publisher, year of publication, first and any change in last page numbers (if relevant):

Moore DC, *Regional Block*, 4th edn. Springfield, Illinois: Charles C Thomas, 1979

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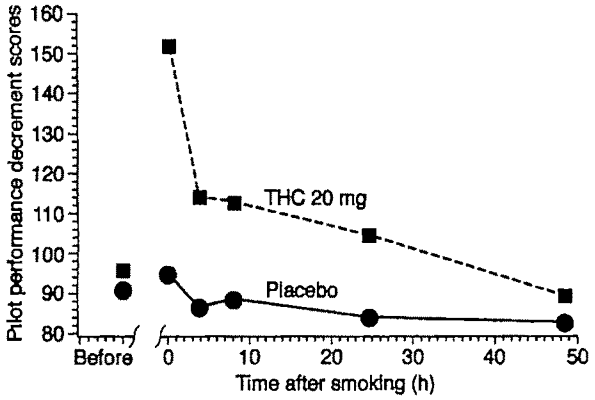

Fig 1 Effect of smoking a cannabis cigarette containing THC 20 mg on pilot performance in flight simulator tasks. Performance on six simulator tasks included in one flight session was standardized to give mean decrement scores; nine pilots performed the tasks under both drug and placebo conditions.[76]

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Spelling, etc. British spelling should be used with 'z' rather than 's' spelling in, e.g. organize, organization.

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Appendix

Common sources of difficulty include the following:

Blood-gases—specify carbon dioxide, P_{CO_2}, etc.

Blood pressure—avoid this term in favour of arterial pressure, etc. Specify mean, systolic, diastolic.

Case—this should not be regarded as interchangeable with the term 'patient'. An account of the management of a patient may be referred to as a 'case history' or 'case report'.

Chronic bronchitics—avoid this expression when you mean patients with chronic bronchitis.

Data—plural.

Demographics—often used incorrectly to refer to patient characteristics.

Due to—avoid unless in the description of a financial debt. *Because of* and *as a result of* are preferable.

Employed—prefer used.

Fall and *Rise*—avoid these expressions which suggest a gravitational influence. *Decrease* or *reduction* and *increase* are preferable.

Groups—avoid expressions such as 'thiopental patients' and 'cholecystectomy patients' in favour of 'patients receiving thiopental' and 'patients undergoing cholecystectomy'. It is permissible, however, to refer to the 'thiopental group' or 'cholecystectomy group'.

High and *Low*—avoid if you mean large and small.

Incidence—this refers to the proportion of a defined group developing a condition within a stated period. *Frequency* is the number of subjects (expressed usually as a percentage) with a condition. *Prevalence* is frequency at one point in time.

Length (of time or drug effect)—prefer *duration*.

Level—avoid in favour of *concentration*.

Multiple adjectives—avoid using an adjective in apposition to a noun, e.g. 'concentration of sodium' is preferable to 'sodium concentration'.

Postoperatively and *preoperatively*—prefer *after operation* or *before operation*.

Postoperative (preoperative) treatment—acceptable.

Relaxants—avoid in favour of 'neuromuscular blocking drugs'.

Rotameter—note capital letter.

Sacrifice—this is ritualism. Killed is preferable.

Showed—prefer *was present* or *occurred*.

Significant—avoid expressions such as 'highly significant' or 'very highly significant', in favour of *significant* with a probability value in brackets.

Sleep-dose—this is vague. Prefer *a dose sufficient to abolish the eyelash reflex, etc.*

Stable (of measurements)—prefer *unchanged* or *virtually unchanged*.

Teflon—note capital letter

Tendency to change-changed.

It is important to avoid conversational expressions such as:

'the patient was ventilated' (the lungs were ventilated)

'the patient was intubated' (the trachea was intubated)

'the patient was placed on a ventilator' (ventilation was controlled artificially)

'the patient was taken off the ventilator' or 'the patient was weaned from the ventilator' (artificial ventilation was discontinued)

'the patient was extubated' (the tracheal tube was removed).

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International Journal of Anaesthesia
Volume 88 Number 2 February 2002

EDITORIALS

159 I. Is there a bleeding problem with platelet active drugs?
T. Kövesi and D. Royston

163 II. Rapacuronium: why did it fail as a replacement for succinylcholine?
P. F. White

CLINICAL INVESTIGATIONS

166 Can molecular similarity-activity models for intravenous general anaesthetics help explain their mechanism of action?
J. C. Sewell and J. W. Sear

175 Model-based administration of inhalation anaesthesia. 4. Applying the system model
J. G. C. Lerou, R. Verheijen and L. H. D. J. Booij

184 Bispectral index monitoring during electroconvulsive therapy under propofol anaesthesia
P. O. Gunawardane, P. A. Murphy and J. W. Sleigh

188 Effect of hypothermia on brain tissue oxygenation in patients with severe head injury
A. K. Gupta, P. G. Al-Rawi, P. J. Hutchinson and P. J. Kirkpatrick

193 Cardiovascular effects of simultaneous occlusion of the inferior vena cava and aorta in patients treated with hypoxic abdominal perfusion for chemotherapy
J. Hofland, R. Tenbrinck, M. G. A. van IJken, C. H. J. van Eijck, A. M. M. Eggermont and W. Erdmann

199 Comparative effect of paracetamol, NSAIDs or their combination in postoperative pain management: a qualitative review
M. Hyllested, S. Jones, J. L. Pedersen and H. Kehlet

215 Rectal and parenteral paracetamol, and paracetamol in combination with NSAIDs, for postoperative analgesia
J. Rømsing, S. Møiniche and J. B. Dahl

227 Ketorolac, diclofenac, and ketoprofen are equally safe for pain relief after major surgery
J. B. Forrest, F. Camu, I. A. Greer, H. Kehlet, M. Abdalla, F. Bonnet, S. Ebrahim, G. Escolar, J. Jage, S. Pocock, G. Velo, M. J. S. Langman, G. Bianchi Porro, M. M. Samama and E. Heitlinger for the POINT investigators

234 Comparison of predictive models for postoperative nausea and vomiting
C. C. Apfel, P. Kranke, L. Eberhart, A. Roos and N. Roewer

241 Depth of sedation in children undergoing computed tomography: validity and reliability of the University of Michigan Sedation Scale (UMSS)
S. Malviya, T. Voepel-Lewis, A. R. Tait, S. Merkel, K. Tremper and N. Naughton

246 Positive pressure ventilation during fibreoptic intubation: comparison of the laryngeal mask airway, intubating laryngeal mask and endoscopy mask techniques
K. Aoyama, E. Yasunaga, I. Takenaka, T. Kadoya, T. Sata and A. Shigematsu

LABORATORY INVESTIGATIONS

255 Differential effects of intravenous anaesthetic agents on the response of rat mesenteric microcirculation *in vivo* after haemorrhage
Z. L. S. Brookes, N. J. Brown and C. S. Reilly

264 Xenon produces minimal haemodynamic effects in rabbits with chronically compromised left ventricular function
B. Preckel, W. Schlack, T. Heibel and H. Rütten

REVIEW ARTICLE

270 Analgesia for pelvic brachytherapy
M. D. Smith, J. G. Todd and R. P. Symonds

SHORT COMMUNICATIONS

277 Effects of temperature and haematocrit on the relationships between blood flow velocity and blood flow in a vessel of fixed diameter
O. Paut and B. Bissonnette

280 Improvement of information gained from the pre-anaesthetic visit through a quality-assurance programme
S. Ausset, H. Bouaziz, M. Brosseau, B. Kinirons and D. Benhamou

283 How reliable is length-based determination of body weight and tracheal tube size in the paediatric age group? The Broselow Tape reconsidered
C. K. Hofer, M. Ganter, M. Tucci, R. Klaghofer and A. Zollinger

285 Effect of spinal anaesthesia on plasma concentrations of glutathione S-transferase
D. C. Ray, A. G. Robbins, A. F. Howie, G. J. Beckett and G. B. Drummond

CASE REPORTS

288 Submental intubation in a patient with beta-thalassaemia major undergoing elective maxillary and mandibular osteotomies
P. H. K. Mak and R. G. B. Ooi

291 Management of life-threatening haemoptysis
E. Håkanson, I. E. Konstantinov, S.-G. Fransson and R. Svedjeholm

296 Mechanical closure of the vocal cords with the laryngeal mask airway ProSeal™
J. Brimacombe, C. Richardson, C. Keller and S. Donald

298 Infected mediastinitis secondary to perforation of superior vena cava by a central venous catheter
P. Valat, C. Pellerin, O. Cantini, J. Jougon, F. Delcambre, P. Morales and G. Janvier

301 CORRESPONDENCE

312 BOOK REVIEWS

314P Proceedings of the Anaesthetic Research Society, University of Nottingham, November 22–23, 2001

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We interrupt this to bring you a very important message:
By the time you've read this, someone will have died from sepsis.

Recent analyses conducted by ICNARC (the Intensive Care National Audit & Research Centre) on data collected from 92 adult general ICUs[†] have shown that the prevalence of severe sepsis[‡] during the first 24 hours in the ICU is 27.7%[§1]. In England and Wales (excluding Northern Ireland and Scotland), this figure potentially represents a prevalence of 21,033[§1] severe sepsis cases during the first 24 hours in the ICU out of a total adult general ICU caseload of 73,203[§1].

Severe sepsis is a major cause of morbidity and mortality. In adults, severe sepsis has been associated with mortality rates ranging from 28% to 50%[2] and these rates have remained unchanged for several decades. For the 92 adult general ICUs included in the Case Mix Programme Database, the associated overall hospital mortality for severe sepsis in England, Wales and Northern Ireland is 44.7%[§1].

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References
1. Eli Lilly and Company Data on file Source of data The Intensive Care National Audit & Research Centre 2. Natanson C et al Crit Care Med 1998,26 1927–31

† throughout England, Wales and Northern Ireland, ‡ defined as sepsis associated with acute organ dysfunction, § these figures do not include cases of severe sepsis that occur either on wards or after the first 24 hours in the ICU

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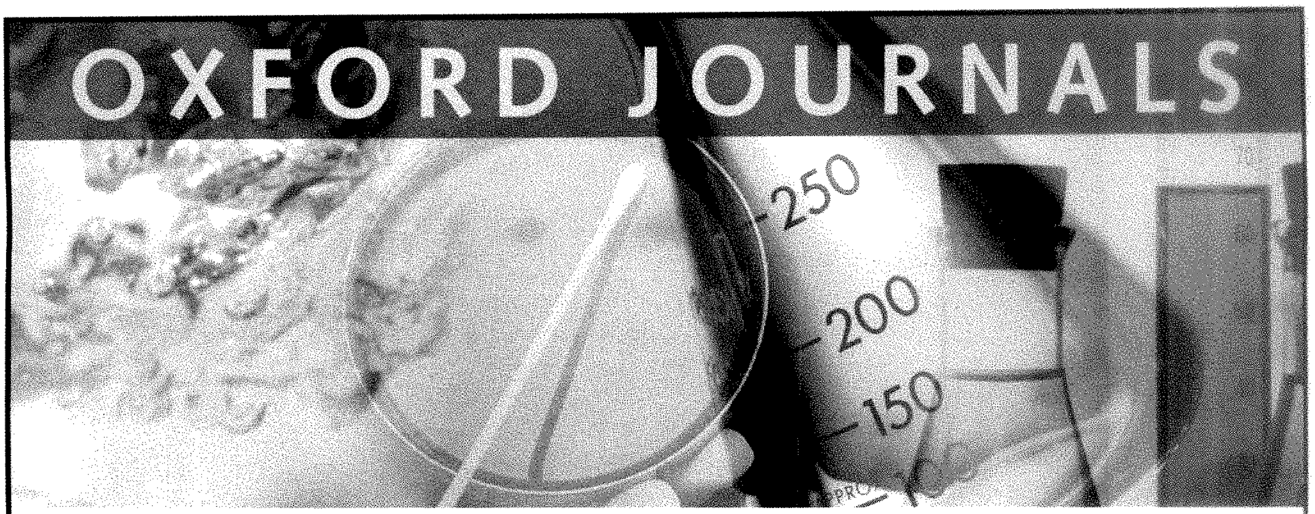

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BJA CEPD Reviews is a joint venture of the British Journal of Anaesthesia and The Royal College of Anaesthetists in collaboration with the Intensive Care Society and Pain Society.

The purpose of ***BJA CEPD Reviews*** is the publication of material to support the continuous medical education and professional development of specialists in anaesthesia, critical care medicine and pain

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PAIN

KILL

VIOXX®ACUTE ▼
(rofecoxib)
ABRIDGED PRODUCT INFORMATION

Refer to Summary of Product Characteristics before prescribing

PRESENTATION

Tablets: 25 mg and 50 mg tablets each containing 25 mg or 50 mg of rofecoxib.

USES

Relief of acute pain. Treatment of primary dysmenorrhoea.

DOSAGE AND ADMINISTRATION

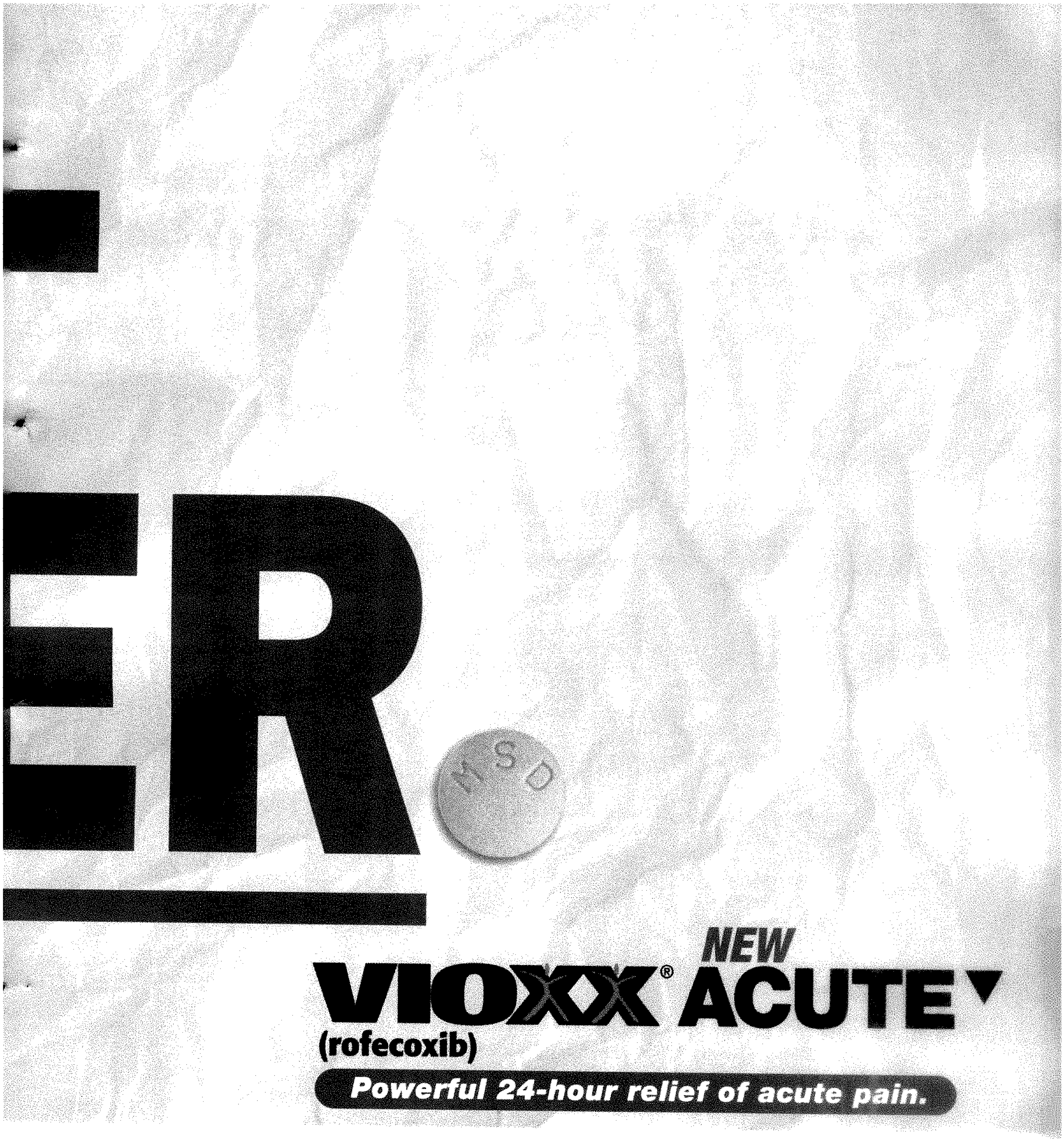
The recommended adult initial dose is 50 mg once daily, orally, with or without food. Subsequent doses should be 25 or 50 mg once daily. The maximum recommended daily dose is 50 mg. Use for the acute symptomatic period only. *Elderly:* It is prudent to use the lowest recommended dose and exercise caution in the treatment of elderly patients. *Renal insufficiency:* no dosage adjustment is necessary for patients with creatinine clearance 30-80 ml/min. *Children:* not indicated.

CONTRA-INDICATIONS

Hypersensitivity to any excipient of this product. Active peptic ulceration or gastro-intestinal (GI) bleeding. Hepatic dysfunction. Estimated creatinine clearance <30 ml/min. Patients who have developed asthma, acute rhinitis, nasal polyps, angioneurotic oedema or urticaria after aspirin or other NSAIDs. Third trimester of pregnancy and lactation. Inflammatory bowel disease. Severe congestive heart failure.

PRECAUTIONS

Consider monitoring renal function in patients with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis. Use caution when initiating treatment in patients with considerable dehydration. Rehydrate patients prior to starting therapy with rofecoxib. Consider the possibility of fluid retention and exercise caution when rofecoxib is used in patients with pre-existing oedema, a history of heart failure, left ventricular dysfunction or hypertension. Maintain appropriate supervision when treating the elderly or patients with renal, hepatic or cardiac dysfunction with rofecoxib. Rofecoxib may mask fever. Use of rofecoxib is not recommended in women attempting to conceive. In clinical studies, some osteoarthritis (OA) patients treated with rofecoxib developed perforations, ulcers or bleeds (PUBs). Patients with a prior history of a PUB and patients greater than 65 years of age appeared to be at a higher risk for a PUB. At chronic daily doses higher than 25 mg, the risks of gastro-intestinal symptoms, oedema or hypertension are increased. Elevations of ALT and/or AST (≥3 times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with rofecoxib. Any patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated. *Interactions (pharmacodynamic): Warfarin:* closely monitor the prothrombin time INR when therapy with
rofecoxib is initiated or changed in patients receiving warfarin or similar agents, particular
first few days. *ACE-inhibitors:* administration of 25 mg daily of rofecoxib with benazepri
to 40 mg daily for four weeks to patients with hypertension was associated with a small att
of the antihypertensive effect compared to the ACE inhibitor alone. This should be consi
patients taking rofecoxib concomitantly with ACE inhibitors. *Beta-blockers and diuretics:* con
use of NSAIDS may reduce the antihypertensive efficacy of beta-blockers and diuretics and
effects of diuretics. *Aspirin:* at steady state, rofecoxib 50 mg once daily had no effect on
platelet activity of low-dose (81 mg once daily) aspirin. Avoid concomitant administration of r
with higher doses of aspirin or other NSAIDS. *Cyclosporin/tacrolimus:* monitor renal functi
rofecoxib and either cyclosporin or tacrolimus is used in combination. *Interactions (pharma*
Lithium: NSAIDS may increase plasma lithium concentrations. *Methotrexate:* consider
monitoring for methotrexate-related toxicity when rofecoxib and methotrexate are adm
concomitantly. *CYP1A2 substrates:* exercise care with concomitant administration of rofec
drugs primarily metabolised by CYP1A2 (e.g. theophylline, amitriptyline, tacrine and
Midazolam: a modest 30% reduction of the AUC of midazolam was seen with rofecoxib 25
most likely due to increased first pass metabolism through induction of intestinal CYP3A
by rofecoxib. *CYP3A4 substrates:* in spite of a modest induction of intestinal CYP3A4 act
pharmacokinetics of drugs metabolised primarily by CYP3A4 are not expected to be affe
clinically significant extent. However exercise care when co-prescribing substrates of CYP



Rifampicin: co-administration of rofecoxib with rifampicin, a potent inducer of CYP
produced an approximate 50% decrease in rofecoxib plasma concentrations. Therefore,
ıe highest dose when rofecoxib is used with potent inducers of hepatic metabolism. Based
data, rofecoxib is not expected to inhibit cytochromes P450, 2C9, 2C19, 2D6 or 2E1.
: Do not use in the last trimester of pregnancy, because like other prostaglandin synthesis
ofecoxib may cause uterine inertia and premature closure of the ductus arteriosus. Rofecoxib
be used during the first two trimesters of pregnancy unless the benefit to the patient
the risk to the foetus. *Lactation:* contra-indicated.

FECTS

ring drug-related undesirable effects were reported at an incidence greater than 1% and
ın placebo in analgesia clinical studies in patients treated with rofecoxib 50 mg or 25 mg
lays: dizziness, diarrhoea, diaphoresis, dyspepsia. The following drug-related undesirable
re reported at an incidence greater than placebo in osteoarthritis clinical studies in patients
th rofecoxib 12.5 mg or 25 mg for up to six months, or in post-marketing experience.
*(≥1/100, <1/10); Uncommon (≥1/1000, <1/100), Rare (≥1/10,000, <1/1000); Very
10,000) and isolated cases]*

whole/site unspecified: *Common:* oedema/fluid retention, abdominal pain, dizziness.
ı: asthenia/fatigue, abdominal distension, chest pain. *Very rare:* hypersensitivity reactions,
ngioedema, urticaria and anaphylactic/anaphylactoid reactions. ***Blood and the lymphatic system disorders:*** *Common:* haematocrit decreased. *Uncommon:* haemoglobin decreased, erythrocytes decreased, leukocytes decreased. *Very rare:* thrombocytopenia. ***Cardiovascular system:*** *Common:* hypertension. *Very rare:* congestive heart failure. ***Digestive system:*** *Common:* heartburn, epigastric discomfort, diarrhoea, nausea, dyspepsia. *Uncommon:* constipation, oral ulcer, vomiting, digestive gas symptoms, acid reflux. *Rare:* peptic ulcers, gastro-intestinal perforation and bleeding (mainly in elderly patients), gastritis. ***Hepatobiliary disorders:*** *Common:* alanine aminotransferase increased, aspartate aminotransferase increased. *Uncommon:* alkaline phosphatase increased. *Isolated cases:* hepatotoxicity including hepatitis and jaundice. ***Eyes, ears, nose and throat:*** *Uncommon:* tinnitus. *Very rare:* blurred vision. ***Metabolism and nutrition:*** *Uncommon:* weight gain. ***Musculoskeletal:*** *Uncommon:* muscular cramp. ***Nervous system:*** *Common:* headache. *Uncommon:* insomnia, somnolence, vertigo. *Very rare:* paraesthesia. *Isolated cases:* aseptic meningitis. ***Psychiatric disorder:*** *Uncommon:* depression, mental acuity decreased. *Very rare:* confusion, hallucinations. ***Respiratory system:*** *Uncommon:* dyspnoea. *Very rare:* bronchospasm. ***Urogenital:*** *Uncommon:* BUN increased, serum creatinine increased, proteinuria. *Very rare:* renal insufficiency, including renal failure, usually reversible upon discontinuation of therapy. ***Skin and skin appendages:*** *Common:* pruritus. *Uncommon:* rash, atopic dermatitis. *Very rare:* alopecia. *Isolated cases:* cutaneo-mucosal adverse effects and severe skin reactions including Stevens-Johnson Syndrome. In clinical studies, the undesirable effects profile was similar in patients treated with rofecoxib for one year or longer. The following serious adverse effects have been reported in association with the use of NSAIDs and cannot be ruled out for rofecoxib: nephrotoxicity including interstitial nephritis and nephrotic syndrome, hepatotoxicity including hepatic failure.

PACKAGE QUANTITIES AND BASIC NHS COST

25 mg: packs of 14 tablets: £10.79. 50 mg: packs of 7 tablets: £5.39

Marketing Authorisation numbers: Tablet 25 mg: PL 0025/0408. Tablet 50 mg: PL 0025/[illegible]

Marketing Authorisation holder: Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, UK

POM **Date of review:** August 2001

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EPREX® ABBREVIATED PRESCRIBING INFORMATION

Please refer to Summary of Product Characteristics (SmPC) before prescribing.

Presentation:
Epoetin alfa solution presented as 1,000 IU/0.5 ml, 2,000 IU/0.5 ml, 3,000 IU/0.3 ml, 4 000 IU/0.4 ml and 10,000 IU/ml in pre-filled syringes and 1,000 IU/0.5 ml, 2,000 IU/ml, 4,000 IU/ml and 10,000 IU/ml in vials. For subcutaneous (SC) injection.

Uses:
To increase autologous blood yield from adult patients in a predonation (ABD) programme (treat only patients with moderate anaemia if blood saving procedures not available or insufficient, when scheduled major elective surgery requires large blood volume). To reduce exposure to allogeneic blood tranfusions prior to major elective orthopaedic surgery (restrict use to patients with moderate anaemia, not having ABD, with expected moderate blood loss).

Dosage and administration:
ABD: IV route. Mildly anaemic patients (haematocrit 33-39%) requiring predeposit of ≥4 blood units: 600 IU/kg 2 times weekly for 3 weeks after the blood donation procedure, prior to surgery. Iron supplementation required.

Elective orthopaedic surgery: SC route. 600 IU/kg weekly three weeks prior to surgery and on surgery day. Where surgery lead time <3 weeks, 300 IU/kg ten consecutive days prior to surgery, on surgery day and for 4 days immediately after. Stop treatment if Hb level reaches 15 g/dl. Iron supplementation required.

Contra-indications:
Uncontrolled hypertension. All ABD programmes' contra-indications. Component hypersensitivity. Prior to major elective orthopaedic surgery in patients (not participating in an ABD programme) with severe coronary, peripheral arterial, carotid or cerebral vascular disease, including those with recent myocardial infarction or cerebral vascular accident. Patients who cannot receive adequate antithrombotic prophylaxis.

Warnings and precautions:
Closely monitor blood pressure. Epilepsy and chronic liver failure–use with caution. Consider and treat all other causes of anaemia before starting EPREX. Mostly, serum ferritin falls simultaneously with packed cell volume rise. Assure adequate iron stores to ensure optimum EPREX response. Monitor platelet count regularly during first 8 weeks. Epoetin alfa cannot be excluded as possible growth factor for any tumour type. Respect special warnings associated with ABD programme. Prior to elective orthopaedic surgery–establish anaemia cause and determine thromboembolic risk/benefit. Give adequate antithrombotic prophylaxis. If Hb >13 g/dl do not use; increased risk of thrombotic vascular events.

Use in pregnancy and lactation only if potential benefit outweighs potential risk to foetus or baby.

Side effects:
Nonspecific skin rashes and flu-like symptoms. Increased risk of thrombotic/vascular events where Hb >13 g/dl prior to elective orthopaedic surgery.

Overdosage:
High therapeutic margin. Phlebotomy may be performed if Hb too high.

Interactions:
Do not administer with other drug solutions. Potential cyclosporin interaction. No interaction evidence with G-CSF or GM-CSF.

Pharmaceutical precautions:
Store at 2 to 8°C. Do not freeze or shake. Protect from light. Unpreserved product. Administer only one dose per vial or syringe.

Legal category: POM

Product licence/authorisation holder:
Janssen-Cilag Ltd, Saunderton, High Wycombe, Buckinghamshire, HP14 4HJ, UK. (PL/0242/0215, 0218, 0221, 0297-9 PA/748/25/1-9)

Date of preparation: February 2000

Further information: Available from:
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References:

1. Stowell CP, Chandler H, Jové M, Guilfoyle M, Wacholtz MC. *Orthopedics.* 1999;22(suppl 1):s105-s112.
2. de Andrade JR, Jove M, Landon G, Frei D, Guilfoyle M, Young DC. *Am J Orthop.* 1996;25:533-542.
3. Keating EM, Ranawat CS, Cats-Baril W. *Orthopedics.* 1999;22(suppl 1):s119-s128.

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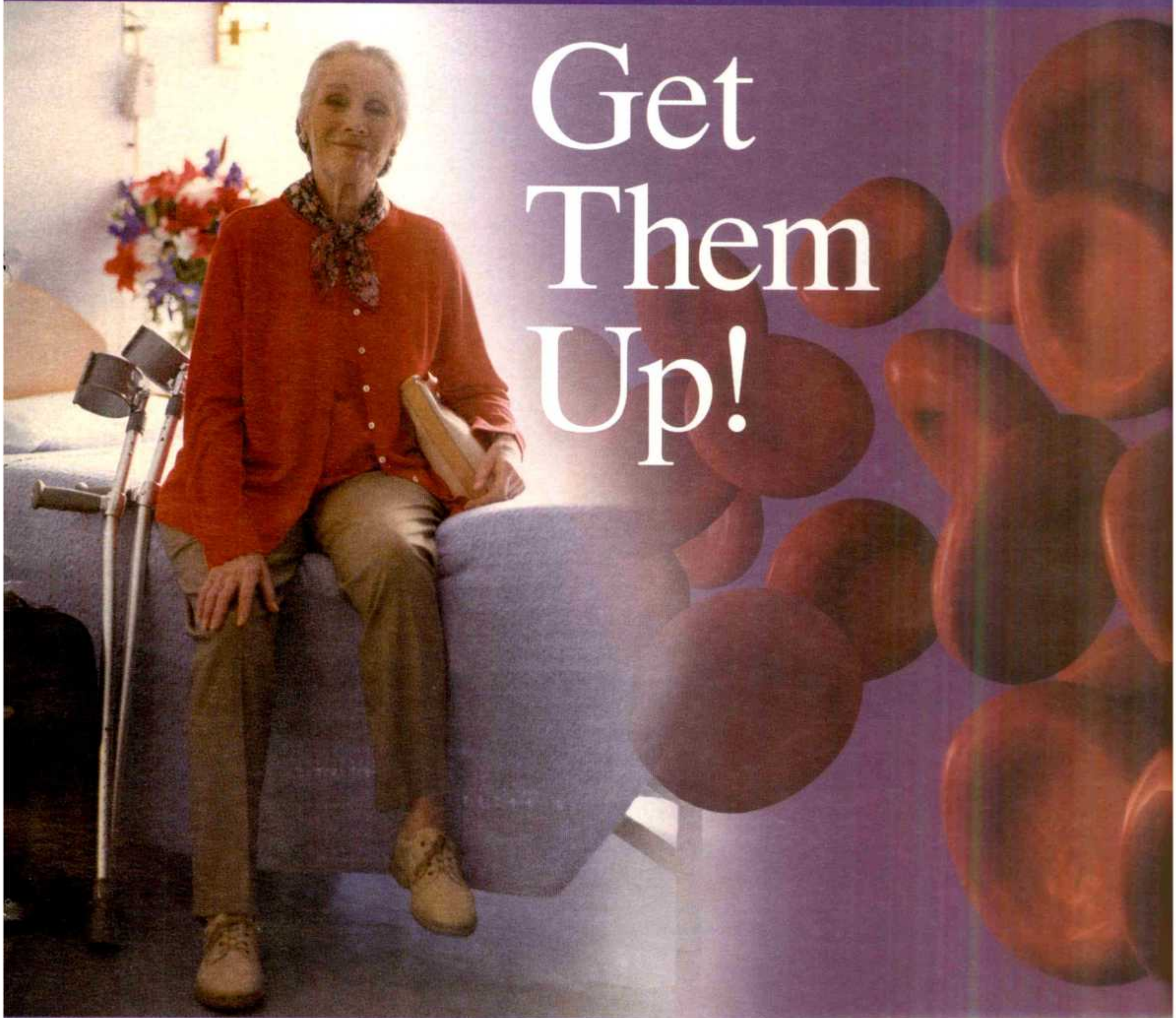

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Editorial Notices

$500,000 IARS Frontiers in Anesthesia Research Award—Fourth Recipient

The Board of Trustees of the International Anesthesia Research Society (IARS) announced at the 75th Clinical and Scientific Congress the fourth recipient of the $500,000 IARS Frontiers in Anesthesia Research Award. The award was established by the IARS in 1994 'to foster innovation and creativity by an individual scientist in the field of Anesthesiology'. The fourth recipient is:
Mark A. Schumacher, PhD, MD, University of California, San Francisco, California.

Dr Schumacher's research project is titled 'Stretch-Inactivated Channels in Pain Transduction'. Dr Schumacher is an Assistant Professor in the Department of Anesthesia and Perioperative Care at the School of Medicine, University of California, San Francisco.

10th Winter Symposium on Intensive Care Medicine

Crans Montana, Switzerland, February 3–8, 2002

For further details, please contact: Mrs Veronique De Vlaeminck, Department of Intensive Care – Symposium, Erasme University Hospital, Route de Lennik 808, B-1070 Brussels, Belgium. Tel: +32 2 555 47 57; Fax: +32 2 555 45 55; Email: sympicu@ulb.ac.be

The Mersey School, Anaesthesia and Perioperative Medicine and The Section of Anaesthesia, The Royal Society of Medicine For Anaesthetists only: Challenge, Concern, Frustration and Despair—Performance, Risk Management, Appraisal and Revalidation

The Liverpool Maritime Museum, Liverpool, UK, February 6, 2002, 9.30–16.30

For further details, please contact: Dr D. Gray, Potgraduate Medical Centre, Broadgreen Hospital, Liverpool L14 3LB, UK. Tel: +44 (0)151 529 5809

9th Annual Paediatric Anaesthesia Update

The Manchester Conference Centre, Weston Building, Sackville Street, Manchester, UK, February 15, 2002

A repetition of this highly successful CME approved course, with a selection of topical reviews intended for consultant and trainee anaesthetists with an interest in paediatric anaesthesia.

Fee: £150 includes coffee, lunch, tea and course booklet.
For further information please contact: The Secretary, University Department of Anaesthesia, Royal Manchester Children's Hospital, Hospital Road, Pendlebury, Manchester, M27 4HA, UK. Tel/Fax: +44 (0)161 727 2291. Email: jonespa@zoom.co.uk

Legal and Ethical Issues in Anaesthesia and Critical Care

Clinical Education Centre, Glenfield Hospital, Leicester, February 22, 2002

For further information please contact: Conference Co-ordinator, Clinical Education Centre, Glenfield Hospital, Groby Road, Leicester LE3 9QP, UK. Tel: +44 (0)116 250 2305; Fax: +44 (0)116 256 3334; Email: jackie.howarth@uhl-tr.nhs.uk

International Anaesthesia Research Society Annual Clinical and Scientific Congresses

March 16–20, 2002
IARS 76th Clinical and Scientific Congress, San Diego Marriott Hotel & Marina, San Diego, California, USA.

March 22–26, 2003
IARS 77th Clinical and Scientific Congress, New Orleans Marriott, New Orleans, Louisiana, USA.

March 27–31, 2004
IARS 78th Clinical and Scientific Congress, Tampa Marriott Waterside Hotel, Tampa, Florida, USA.

March 11–15, 2005
IARS 79th Clinical and Scientific Congress, Hilton Hawaiian Village, Honolulu, Hawaii, USA.

Contact information: IARS, 2 Summit Park Drive, Suite 140, Cleveland, OH 44131, USA. Tel: +1 216 642 1124; Fax: +1 216 642 1127; E-mail: iarshq@iars.org; Web: www.iars.org

22nd International Symposium on Intensive Care and Emergency Medicine

Congress Center, Brussels, Belgium, March 19–22, 2002

For further details, please contact: Mrs Veronique de Vlaeminck, Department of Intensive Care, Erasme University Hospital, Route de Lennik 808, B-1070 Brussels, Belgium. Tel: +32 2 555 32 15/36 31; Fax: +32 2 555 45 55; Email: Veronique.De.Vlaeminck@ulb.ac.be
Website: http://www/intensive.org

Primary FRCA Revision Course

Clinical Education Centre, Glenfield Hospital, March 20–22, 2002

An intensive revision course for the Primary FRCA based on small group tutorials and including written and oral examination practice.

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Fees: £250 non-residential (including lunch and refreshments). Places are strictly limited.
For a booking form, please contact: Christine Gethins. Tel: +44 (0)116 258 5291; E-mail: anae@le.ac.uk

Final FRCA Revision Course

Leicester Royal Infirmary, April 8–11, 2002

An intensive revision course for the Final FRCA based on small group tutorials and including written and oral examination practice.

Fees: £290 including lunch and refreshments; £335 with 3 nights accommodation; £350 with 4 nights accommodation. Places are strictly limited.
For a booking form, please contact: Christine Gethins. Tel: +44 (0)116 258 5291; E-mail: anae@le.ac.uk.

Advances in Minimally Invasive Hand/Upper Extremity Surgery

Genval (Brussels), Belgium, April 19–20, 2002

The symposium will promote exchange between scientists and clinicians, and will include presentations by invited faculty. Participants may submit original papers for a limited number of oral presentations, and there will be considerable time reserved for discussion. Deadline for submission of abstracts: December 31, 2001.

For further details, please contact: F. Schuind, MD, PhD, Department of Orthopaedics, Erasme University Hospital, 808 route de Lennik, B-1070 Brussels, Belgium. Tel: +32 2 555 68 44/36 45; Fax: +32 2 520 35 56: E-mail: fschuind@ulb.ac.be

Artificial Oxygen-carriers: a Clinical Future?

The Royal College of Physicians of Edinburgh, Edinburgh, May 9, 2002

Speakers to include Dr John Hess, Professor Donat Spalm, Dr J. Maguire and Dr Dafydd Thomas. With contributions from the major companies attending a prior workshop.

For further details, please visit the website: http://www.rcpe.ac.uk/AOCs or Tel: +44 (0)131 225 7324; Fax: +44 (0)131 220 4393

Putting New Flesh on Old Bones: a major conference on Issues in the Perioperative Care of Geriatric Trauma

The Netherwood Hotel, Grange-Over-Sands, UK, May 10, 2002

Speakers include: Nigel Sharrock (New York); Martyn Parker (Peterborough)

Deadline for free paper abstracts: February 1, 2002.

Please contact Dr Andrew Severn for details: Tel: +44 (0)1524 583517; Fax: +44 (0)1524 583519.

Australian and New Zealand College of Anaesthetists Annual Meeting

Brisbane Convention and Exhibition Centre, Brisbane, Australia, May 11–15, 2002

For further information please contact:

ANZCA 2002 Secretariat, PO Box 1280, Milton QLD 4064, Australia.

Tel: +61 (0) 7 3858 5537; Fax: +61 (0) 7 3858 5510;
E-mail: anzca2002@im.com.au; Website: www.anzca.edu.au

Royal Australasian College of Surgeons and The Royal College of Surgeons of Edinburgh, Annual Scientific Congress

Adelaide, Australia, May 11–15, 2002

A joint meeting of the colleges to celebrate the 75th anniversary of the Australasian College. A team of speakers will address: Clinical Governance, Quality in Surgical Education, Remote and Rural Surgery, Medical Legal Problems, Colorectal Surgery, Paediatric Surgery, and Trauma.

Closing date for abstracts: January 25, 2002. Abstracts should be submitted electronically: http://www.surgeons.org

Registration for Fellows of the Royal College of Surgeons of Edinburgh will be through this College. Please contact: Mrs Maureen Lowrie in the Education Section of the College. Tel: +44 (0)131 668 9209; Fax: +44 (0)131 668 9241. Email: m.lowrie@rcsed.ac.uk

First World Congress on Regional Anaesthesia and Pain Therapy

Barcelona, Spain, June 5–8, 2002

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; Email: dionne@options.com.cy

XVIth Edinburgh Anaesthesia Festival

Edinburgh, UK, August 21–23, 2002

A three-day programme consisting of lectures and discussion on current topics in anaesthesia.

For further details, please contact: University Department of Anaesthesia, Critical Care and Pain Medicine, Royal Infirmary, Lauriston Place, Edinburgh EH3 9YW, UK.

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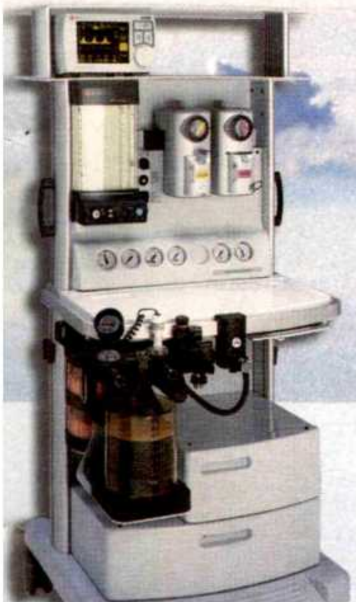

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Anaesthesia outside the square: CECANZ Conference 2002

Christchurch, New Zealand, September 18–20, 2002

For information, please contact: Conference Secretariat Joy Mehlhopt, Conference Innovators, P.O. Box 1370, Christchurch, New Zealand.

Tel: +61 3 379 0390; Fax: +61 3 379 0460; E-mail: joy@conference.co.nz. Website: www.cecanz2002.org.nz

Société Française d'Anesthésie et de Réanimation

Annual congresses will take place in Palais des Congrés, Porte Maillot, Paris on the following dates:

September 26–29, 2002
September 18–21, 2003
September 20–October 3, 2004
September 29–October 2, 2005

For further information, please contact: SFAR, 74, rue Raynouard, F-75016 Paris, France. Tel: +33 1 45 25 82 25; Fax: +33 1 40 50 35 22; E-mail SFAR@invivo.edu

Dingle 2002—4th Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 2–6, 2002

For further information contact: Dr Monty Mythen, Director, Centre for Anaesthesia, UCL, Room 103, 1st Floor Crosspiece, Middlesex Hospital, London, W1T 3AA, London, UK. Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com

Australian Society of Anaesthetists National Scientific Congress

Adelaide, Australia, October 26–30, 2002

This is the Society's premier scientific conference, held in an interesting part of the world.

For further details, please contact: Festival City Conventions, P.O. Box 949, Kent Town, S.A. 5071, Australia. Tel: +61 (0)8 8363 1307; Fax: +61 (0)8 8363 1604: E-mail: asa2002@fccconventions.com.au

8th International Congress of Cardiothoracic and Vascular Anesthesia
19th International Congress of the Israel Society of Anesthesiologists

Jerusalem, Israel, November 10–13, 2002

For further information regarding the Congress, please contact:

8th International Congress of Cardiothoracic and Vascular Anesthesia, PO Box 50006, Tel Aviv 61500, Israel

Tel: +972 3 5140000; Fax: +972 3 5140077; E-mail: anesth2002@kenes.com

Web address: http://www.isranest.org.il/congress 2002

German Congress of Anaesthesiology 2002 (DAK 2002)

Messezentrum Nürnberg, June 26–29, 2002

German Congress of Anaesthesiology 2003 (DAK 2003)

Messezentrum Nürnberg, June 18–21, 2003

For further information, please contact:

Medizinisch Congressorganization Nürnberg AG.
Tel: +49 911 393160; Fax: +49 911 331204

27th Congress of The Scandinavian Society of Anaesthesiology and Intensive Care Medicine

Helsinki, Finland, August 16–20, 2003

A biannually arranged Scandinavian congress in one of the five Scandinavian countries; language: English.

For further information please contact: Prof. Per H.Rosenberg, Helsinki University Hospital, Helsinki FIN00029 HUS, Finland.

E-mail: per.rosenberg@hus.fi
Or: CONGREX/Blue & White Conferences Oy

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Web address: www.congrex.fi

Dingle 2003—5th Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 1–5, 2003

For further information contact:

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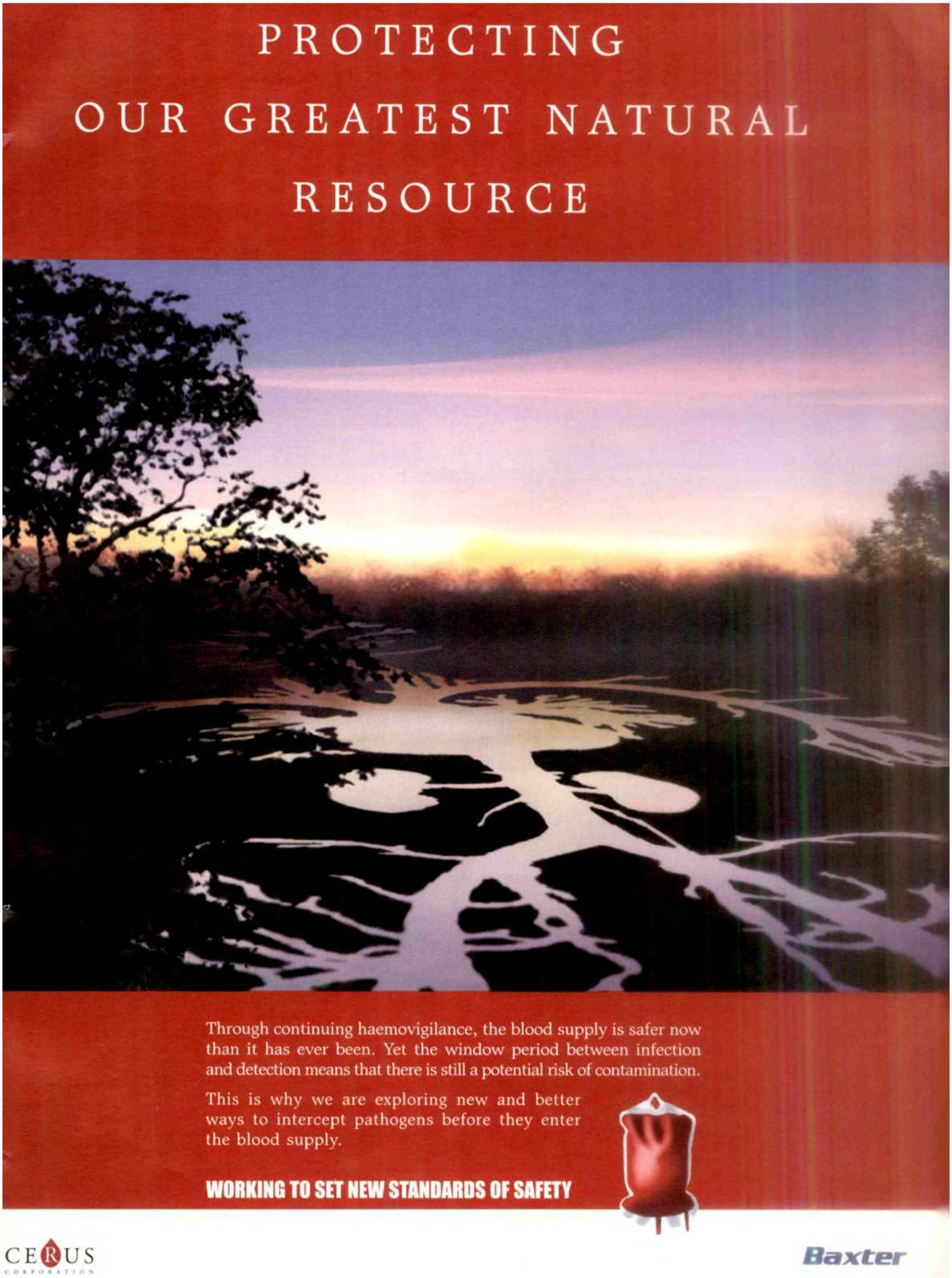

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EDITORIALS

239 Hepatic Autoantibodies, Hepatic Injury, Pediatric Anesthesiologist
241 Urethane: Help or a Hindrance?

PEDIATRIC ANESTHESIA (Society for Pediatric Anesthesia)

243 Occupational Hepatitis, Volatile Anesthetics, and Anesthesiologists
250 Internal Jugular Vein Size in Children
255 CBL Velocity, CO_2 Reactivity, and Laparoscopy
259 Systemic Absorption After Caudal Ropivacaine or Bupivacaine
266 Pediatric Ketorolac Pharmacokinetics
271 Anesthesia in Congenital Insensitivity to Pain and Anhidrosis

CARDIOVASCULAR ANESTHESIA (Society of Cardiovascular Anesthesiologists)

275 Thoracic Epidural Anesthesia for Cardiac Surgery
283 A New Cardiac Aprotinin Dosing Schedule
290 Atrial Fibrillation and Cognitive Decline
296 Sodium Nitroprusside Improves Leukocyte Behavior After Shock
302 Anesthesiologist Intraoperative TEE Interpretation
310 Left Ventricular Outflow Tract Obstruction by TEE (Case Report)

ANESTHETIC PHARMACOLOGY (International Society for Anaesthetic Pharmacology)

313 Mechanism of Urethane Action
319 Local Anesthetics Neurotoxicity
325 Local Anesthetics and NMDA Receptors
331 Lipid Emulsions Activate NMDA Receptors
338 Melatonin and Postoperative Delirium (Case Report)
340 Nitrous Oxide and Diaphragm Contractility

AMBULATORY ANESTHESIA (Society for Ambulatory Anesthesia)

346 Intrathecal Lidocaine-Sufentanil Versus Desflurane
351 Pain on Infiltration with Local Anesthetic
355 Paravertebral Blockade for Minor Breast Surgery
360 Electroconvulsive Therapy and Obesity (Special Article)

TECHNOLOGY, COMPUTING, AND SIMULATION (Society for Technology in Anesthesia)

362 Auditory Display Evaluation
369 ECG Electrodes are Sufficient for BIS Monitoring (Technical Communication)

ECONOMICS AND HEALTH SYSTEMS RESEARCH

372 Applicability of Meta-Analysis Results (Special Article)

CRITICAL CARE AND TRAUMA

378 Crystalloids and Coagulation
385 Anesthetics and Type II Pneumocytes (Brief Report)

NEUROSURGICAL ANESTHESIA

389 SjO_2 During Remifentanil-Based Anesthesia
393 Intracarotid Adenosine—Not Nitroprusside—Increases Cerebral Blood Flow
400 Venous Air Emboli at PEEP Release and Patient Repositioning

OBSTETRIC ANESTHESIA

404 An Evaluation of Sports Drinks During Labor
409 Active Warming During Cesarean Delivery
415 Discitis Associated with Pregnancy and Spinal Anesthesia (Case Report)

PAIN MEDICINE

417 Epidural Infusion Pressure Before and After Epidural Steroid Therapy
421 Phytoestrogens Suppress Chronic Pain in Rats
427 Amitriptyline Effect on Fos in Formalin Test

REGIONAL ANESTHESIA

432 Crystalloid Administration During Spinal Anesthesia
438 Levobupivacaine, Continuous Epidural, and Postoperative Analgesia
445 Cutaneous Distribution of the Obturator Nerve
450 Regional Anesthesia and Bilateral Forearm Surgery (Case Report)

GENERAL ARTICLES

453 Treatment of Postoperative Shivering
461 Screening of Psudocholinesterase Deficiency
467 Modified Nasal Trumpet Maneuver (Technical Communication)
470 Difficult Intubation and Pharyngeal Loop (Case Report)
474 LETTERS TO THE EDITOR
481 BOOK AND MULTIMEDIA REVIEWS

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"I would have everie man write what he knowes and no more."—Montaigne

BRITISH JOURNAL OF ANAESTHESIA

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Editorial I

Is there a bleeding problem with platelet-active drugs?

Platelets provide for primary haemostasis by forming a plug at sites of vascular damage. After initial adhesion, platelets aggregate to effect haemostatic plug formation. Platelet aggregation requires active platelet metabolism; stimulation by agonists such as adenosine diphosphate (ADP) or thrombin; divalent cations; specific plasma proteins such as fibrinogen; and a platelet receptor, the glycoprotein IIb/IIIa (GP IIb/IIIa) complex. Activation of the GP IIb/IIIa receptor on the platelet surface is the final pathway of platelet aggregation, regardless of the initiating stimulus. During aggregation, ADP is released from the platelet to autoactivate its own receptor, thromboxane A_2 (TxA_2) is synthesized, and preformed serotonin is released to promote microvascular constriction, helping the plug to form a more solid hold on wound edges.

Platelet-active medications have diverse mechanisms of action, pharmacodynamic and adverse effect profiles. All the current drugs can prolong the skin bleeding time. One of the perceived risks of platelet active therapy is thus increased bleeding, especially after operative intervention or trauma. This editorial will address the following questions for each separate class of drug:

Is the risk of spontaneous and operative bleeding increased?

What is that risk, based on current literature?

What will be an appropriate intervention to reduce or prevent that risk?

Non-steroidal anti-inflammatory drugs (NSAIDs)

This class of drug can interfere with platelet function by several mechanisms involving inhibition of cyclooxygenase (COX).

Acetylsalicylic acid (the Bayer pharmaceutical company adopted the trade name Aspirin in 1899) is the only NSAID used therapeutically for its antiplatelet action and is the most widely used antiplatelet agent in clinical practice. Acetylation of platelet prostaglandin (PG) synthase by aspirin is irreversible. Its effects on platelet function and bleeding time recover only with the generation of a new population of platelets. The clinically relevant time to accomplish this is still a matter of debate. There is significant individual variability in the duration of haematological response after withdrawal of aspirin therapy. Two recent studies showed that skin bleeding time[1] and platelet aggregation[2] were abnormal for at least 48 h and, in some patients, this abnormality could be measured up to 10 days after withdrawal of therapy.

Spontaneous bleeding

Spontaneous gastric perforation, ulceration and bleeding are a major concern in the use of NSAIDs over a prolonged period. A particularly troublesome problem with NSAID gastropathy is that ulceration is often asymptomatic and frequently presents as perforation or haemorrhage. Although this is less of a problem with the newer COX-2 inhibitors, it is still reported to occur.[3] Conventional therapies with antacids, histamine H_2-receptor antagonists and proton pump inhibitors appear relatively ineffective in preventing NSAID-induced gastropathy. However, tranexamic acid (intravenously or orally) inhibits bleeding and prevents rebleeding.[4]

Surgical bleeding

Despite numerous studies, no firm conclusions can be drawn regarding an increased risk of surgical haemorrhage in haematologically normal patients given NSAIDs. The bulk of studies reported thus far have discussed the role of aspirin in cardiovascular surgery. Reports from the 1980s, which universally report a positive correlation between aspirin ingestion and increased bleeding, have been followed by studies showing no significant effect of aspirin on post-operative bleeding or the need for transfusion, even in higher-risk surgery.[5]

Specific therapy to reduce bleeding

On the basis of the duration of abnormality of haematological tests, it would seem prudent to discontinue aspirin within 48 h of elective surgery. If the patient requires more urgent surgery, there is good evidence that high-dose aprotinin will inhibit bleeding[6] and that desmopressin

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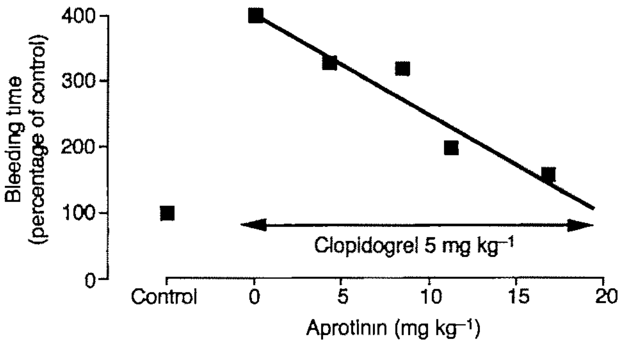

Fig 1 Effect of clopidogrel 5 mg kg^{-1} in increasing bleeding time by 400% and effect of increasing doses of aprotinin on this increase. The line is fitted by least squares regression with y=14.7x+401; r^2=0.92. 1 mg aprotinin=7142 kallikrein inhibitor units. Data are from Herbert and colleagues.[16]

(DDAVP)[7] may also be useful. Interestingly, a recent meta-analysis showed that the use of systemic tranexamic acid had no effect on reducing transfusion requirements after cardiac surgery in patients who received aspirin.[8]

Purinergic or adenosine diphosphate receptor blockers

Adenosine 5′-diphosphate (ADP) is a key cofactor of platelet aggregation. Three separate families of membrane-bound ADP receptors (P2 receptors), with differing structures, mechanisms of action and functions, have been proposed. Currently available data are consistent with shape change being mediated by the high-affinity P2Y1 receptor, aggregation requiring the activation of two receptors.[9] Each of these receptors appears to be essential, and neither is able to trigger aggregation alone.

Clopidogrel (Plavix; Sanofi Winthrop/Bristol-Myers Squibb) and *ticlopidine* (Ticlid; Sanofi Winthrop) are thienopyridine derivatives. Clopidogrel and ticlopidine are licensed for the secondary prevention of vascular events in patients with established atherosclerotic disease (ischaemic stroke, myocardial infarction and peripheral vascular disease).

Neither ticlopidine nor clopidogrel have antiplatelet activity *in vitro* but require metabolism by the hepatic cytochrome P450-1A system. Although their precise mechanism of action has not been identified, their antiplatelet effect appears to result from non-competitive antagonism of a platelet ADP receptor. About 70% of ADP receptors on the platelet are sensitive to the effects of thienopyridines. These are the low-affinity receptors responsible for platelet aggregation and adenylyl cyclase inhibition. The population of high-affinity receptors, presumed to be P2Y1 receptors, is resistant to treatment with clopidogrel.[10] Thromboxane formation is normal, indicating that PG synthase is unaffected. Recovery occurs only with the generation of a new population of platelets, suggesting that antagonism is irreversible.[11]

Spontaneous bleeding

Spontaneous bleeding requiring hospital admission is less frequent in patients treated with thienopyridines than in those treated with aspirin. In an analysis of patients recruited into the CAPRIE study,[12] 205 of 9546 patients (2.15%) treated with aspirin and 169 of 9553 (1.77%) treated with clopidogrel had significant bleeding events. The major difference between the two groups was related to gastro-intestinal bleeding, with 105 hospital admissions associated with aspirin administration compared with 71 with clopidogrel (P=0.012).

Surgical bleeding

The plasma half-life of ticlopidine is 30–55 h and that of clopidogrel is 20–50 h. These times are 2–3 times longer in the older patient.[13] On the basis of this long half-life, it is recommended that clopidogrel is discontinued 7 days and ticlopidine 10–14 days before elective surgery. An increase in postoperative bleeding is reported in patients having cardiac[14] or vascular[15] surgery.

Specific therapy to reduce bleeding

Animal studies have shown that high-dose corticosteroids[13] and aprotinin[16] will partially reverse the effects of thienopyridines on the bleeding time. Aprotinin had no effects on the inhibition of thrombus formation by clopidogrel and its effect on the bleeding time was dose-dependent[16] (Fig. 1). There is no confirmatory evidence of these effects in humans. There is one report of the correction of bleeding time with desmopressin in a ticlopidine-treated patient.[17]

Platelet glycoprotein receptor (GPIIb/IIIa) antagonists

Each platelet glycoprotein integrin is composed of an α and a β subunit. The GPIIb/IIIa complex is the α_{IIb}/β_3 integrin. The interest in integrins stems from identification of their adhesion sites, the best characterized of which is the arginine-glycine-aspartate (RGD) motif,[18] which is ubiquitous among adhesion molecules. The lysine-glycine-aspartate (KGD) sequence is also associated with adhesion but is specific for the fibrinogen receptor.

Three types of inhibitor of the integrin α_{IIb}/β_3 are currently available: abciximab, eptifibatide and tirofiban. All of these are given intravenously with a continuous intravenous infusion after a bolus (loading) dose. Results with all agents suggest that monotherapy is not as effective as combination treatment. For example, three randomized, controlled trials with tirofiban showed efficacy with heparin to be significantly greater than with the drug alone.[19]

Abciximab (c7E3 Fab, ReoPro; Centocor and Eli Lilly) is a non-specific GPIIb/IIIa receptor blocker developed from a mouse-human chimeric 7E3 Fab antibody. The recommended dose regimen produces 80–90% blockade of surface receptors.

Eptifibatide (Integrilin; COR Therapeutics/Schering-Plough) is a synthetic cyclic heptapeptide incorporating the KGD motif. In the UK it is licensed for those with acute coronary syndrome (ACS) in the preceding 24 h who do not fulfil the criteria for thrombolysis. The recommended dose aims to produce a two- to three-fold increase in bleeding time, which is associated with 95% blockade of the GpIIb/IIIa receptor.

The *non-peptide inhibitors* tested thus far use the RGD peptide sequence incorporated into an extraordinarily diverse range of different chemical entities. *Tirofiban* (MK-383, Aggrastat; Merck) is derived from tyrosine. The US Food and Drugs Administration approved this agent for treatment of ACS in 1998.

The efficacy of orally active agents reported thus far is less encouraging. For *sibrafiban* (Xubix; Genentech and Hoffman-La Roche), a recently reported trial showed no significant benefits over the use of aspirin alone in 9233 patients with acute coronary syndrome but major bleeding was more common with high-dose sibrafiban (5.7%) than with aspirin (3.9%).[20]

Spontaneous bleeding

Unless the patient is also receiving heparin or there is thrombocytopenia, spontaneous bleeding is uncommon. The incidence of intracranial bleeding, recorded in 15 850 patients given glycoprotein IIb/IIIa drugs alone, was similar to that with heparin alone (0.07 *vs* 0.06%).[21] However, the risk of bleeding complications at other sites was increased when these agents were given with heparins. One of the earlier studies investigating abciximab[22] reported a two-fold increased risk of major bleeding requiring intervention from sites unrelated to angiography (retroperitoneal, gastrointestinal etc.). However, continued investigation of this agent suggested a lower risk of haemorrhage when a reduced dose of heparin was used (70 U kg^{-1}).[23]

Thrombocytopenia (platelet count less than 100 000 μl^{-1}) occurs with all three drugs. The incidence was about 1 in 40 patients with abciximab;[24] in half of the patients the decrease began 2 h after starting abciximab.[22] Profound thrombocytopenia (platelet count less than 20 000 μl^{-1}) within 24 h of treatment was reported in fewer than 1% of patients and improved spontaneously within 5 days after stopping abciximab. Spontaneous bleeding was more common in patients with thrombocytopenia, and mortality in these patients was also increased from 0.6% in patients with with a normal platelet count to 8.4% ($P<0.001$) in those with a low count.[24] It is recommended that a platelet count should be performed within 2–4 h of instituting therapy as well as 12 and 24 h after starting therapy. Spontaneous bleeding and thrombocytopenia with eptifibatide and tirofiban are of equal concern but may be less of a clinical problem because of the more rapid return of platelet function with these agents.

Surgical bleeding

The focus on procedure-associated bleeding followed early reports of increased bleeding and the need for transfusion after cardiac interventions.[22] As a result of their very effective inhibition of platelet aggregation, this clinical situation has been viewed with considerable concern, and reports of excessive bleeding and large transfusion requirements have been rumoured, reported[25 26] and refuted.[27] Why should there be this inconsistent and apparently contradictory literature?

As with the NSAIDs, the risk of increased postoperative bleeding may be related to the time required to reverse the actions of these agents. In addition to having different receptor affinities, the three agents differ in pharmacodynamic and pharmacokinetic profiles. Abciximab is a high-affinity agent with a very short plasma half-life (30 min) but a prolonged duration of action at the platelet target receptor (time to normal platelet aggregation, 48 h). Eptifibatide and tirofiban are low-affinity agents with a longer plasma half-life (about 100 min) but a relatively short duration of action at the target platelet receptor (time to normal platelet aggregation is about 8 h).

The questions are to define the occupancy of GP IIb/IIIa receptors that is 'safe' and the time to achieve that occupancy. Studies in the relatives of patients with congenital deficiencies show that, with 50% of normal GP IIb/IIIa, there is no evidence of abnormal platelet function or bleeding tendency.[28] Therapeutic intervention aims to achieve 80–90% receptor occupancy, and this is associated with a two- to three-fold prolongation of bleeding time. The 'safe' occupancy must be between these figures.

When abciximab was discontinued, a gradual reduction in receptor blockade occurred. Twelve hours after discontinuation of the drug, about 70% of the receptors were still blocked, but a nearly normal bleeding time has been reported at this level.[29] This process is accelerated with eptifibatide and tirofiban. The bleeding time returns to normal within 1 h of stopping eptifibatide, although return to 50% of baseline platelet aggregation took about 4 h.[30]

Gammie and associates highlighted the importance of the time course of return of platelet functions.[26] Of the 11 patients detailed in their report, six had required coronary artery bypass grafting within 12 h of abciximab treatment. None of the patients died but some did have 'substantial transfusion requirements and, at times, massive coagulopathies'. Median per patient values for blood product transfusions were as follows: red blood cells, 6 units; platelets, 20 units; frozen plasma, 4 units. In contrast, patients who received eptifibatide and required urgent surgery had blood loss and transfusion requirements similar to those of patients who received placebo.[31] This supports the notion of time to recovery of haemostatic function as the principal risk factor.

In order to minimize the risk of bleeding, it would seem logical to allow an appropriate time between discontinuing abciximab and performing surgery. Unfortunately, there is great interpersonal variability in recovery of platelet function.[32] This may also explain some of the differences between the reports of preoperative bleeding in the literature. The residual effects of abciximab can be measured by platelet aggregometry. If this test is abnormal or a further delay is not feasible because of the clinical need of the patient, then what other strategies may be of benefit?

Specific therapy to reduce bleeding

Reduction in the heparin dose, as with invasive cardiology,[23] would seem appropriate for most interventions. There are no reports that confirm this approach as effective or safe during a period of extracorporeal circulation. Low-dose aprotinin therapy did not show efficacy in one report.[25] The therapy with the best supporting literature, according to observations in non-human primates, is to administer platelets. Although free abciximab may not be circulating, that bound to the native platelets redistributes among the total pool, both native and donor, resulting in an overall smaller percentage of blocked receptors. In monkeys, infusion of platelets produced a normal bleeding time within 1 h of the infusion.[27] Clinical experience with routine platelet administration supports the recommendation to administer platelets as an antidote to counteract the effect of recently administered abciximab.[27] To avoid subjecting the donor platelets to the adverse effects of cardiopulmonary bypass, the platelet transfusion should be given after the administration of protamine.

In summary, the evidence for increased risk of spontaneous or perioperative bleeding is not consistent or universal. Withdrawal of therapy before surgery appears to be the only dependable method of reducing any apparent risk. If this is not feasible, certain haemostatic drugs have proven benefits in controlling bleeding associated with NSAIDs and thienopyridines. Administration of platelets appears to be the only intervention likely to be of benefit in patients given GPIIb/IIIa receptor blockers.

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Editorial II

Rapacuronium: why did it fail as a replacement for succinylcholine?

The demise of succinylcholine has been predicted after the introduction of each new short-acting non-depolarizing neuromuscular blocking agent (NMBA). The availability of a rapid- and short-acting non-depolarizing NMBA would clearly enhance the ability of anaesthetists to perform day-surgery procedures on outpatients requiring tracheal intubation, and might facilitate the early recovery process (e.g. fast-tracking) after ambulatory surgery.

After its introduction in the USA, rapacuronium (Raplon; Organon Akzo Nobel, Orange, NJ, USA) was subjected to intense scrutiny because of the current cost-conscious health-care environment and the increasing concern regarding patient safety with all new drugs.[1 2] The challenge facing all anaesthesiologists is to continue to deliver the same high-quality patient care while consuming fewer resources (so-called value-based anaesthesia care). Even though the costs of drugs used for anaesthesia constitute less than 6% of the total cost of perioperative care,[3] they are highly visible and represent an easy target for scrutiny by pharmacy cost-control programmes.

As both mivacurium and rocuronium failed to eliminate the use of succinylcholine because of perceived deficiencies in their onset and/or recovery characteristics,[4] rapacuronium was viewed as a potential replacement for succinylcholine when it was first introduced into clinical practice in 2000. However, as predicted in a 1999 editorial in the *British Journal of Anaesthesia* by Goulden and Hunter,[5] 'succinylcholine has still not reached the end of its active life'. It is now clear that rapacuronium has failed as a 'replacement for succinylcholine' and was recently withdrawn from the US market. This article will discuss some of the possible reasons why this new muscle relaxant failed to achieve acceptance in the US anaesthesia community.

Clinical experience with rapacuronium

Rapacuronium was a non-depolarizing NMBA of the aminosteroid class. In early clinical studies,[6–8] it was alleged to have both a rapid onset and a rapid offset of action, and its effect was also reported to be easily reversible even when the degree of neuromuscular block was still profound. The onset time for block of the laryngeal adductor muscles after an intubating dose of rapacuronium 1.5 mg kg^{-1} was 1.0 (SD 0.2) min,[7] and compared favourably with that of succinylcholine 1.5 mg kg^{-1} [0.9 (0.1) min)] and rocuronium 0.5 mg kg^{-1} [1.4 (0.3) min].[4] Furthermore, rapacuronium was reported to provide good to excellent intubating conditions in 60–90 s,[7 8] which would theoretic-

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ally allow the drug to be used for rapid-sequence intubation of patients considered to be at risk of aspiration during induction of anaesthesia. However, Blobner and colleagues[9] cautioned that succinylcholine clearly provided better intubating conditions than rapacuronium for rapid-sequence induction. The clinical duration of action of rapacuronium after an intubating dose (1.5 mg kg^{-1}) was 14 (6) min,[8] comparable to those of succinylcholine and mivacurium [10 (2) min and 20 (6) min respectively].[4] Moreover, the time for the train of four (TOF) to return to 0.7 (i.e. to achieve clinical recovery) after rapacuronium was similar to that for mivacurium, and clearly longer than that for succinylcholine.[4 8] Depending on the primary maintenance anaesthetic,[10] muscle relaxant activity after an intubating dose of rapacuronium typically persisted for 30–60 min.

While rapacuronium was found to produce more rapid spontaneous recovery of neuromuscular function than other NMBAs of the aminosteroid class[11] and its duration of action could be reduced by reversal with anticholinesterase drugs,[6 12 13] it was still not really comparable to succinylcholine.[4] For example, Purdy and colleagues[12] reported that the neostigmine-assisted recovery time of rapacuronium to a TOF of 0.7 required almost 20 min, significantly longer than the spontaneous recovery time of succinylcholine.[4 6 12 14] It was also unclear whether the spontaneous and/or anticholinesterase-assisted reversal of rapacuronium's relaxant effects facilitated, or actually impeded, the fast-tracking recovery process.[15] Furthermore, spontaneous recovery after a 1 h infusion (or multiple top-up doses) of rapacuronium can be prolonged,[16] analogous to the time-course of an intermediate-acting NMBA.

By replacing succinylcholine in the ambulatory setting, the well-known side-effects of the latter drug could be avoided.[4 5] However, the side-effects of succinylcholine (e.g. myalgias, hyperkalaemia, malignant hyperthermia) should not be replaced by other potentially serious side-effects (e.g. bronchospasm).[17] Although the overall incidence of bronchospasm was allegedly to be 'only' 3.4% in the 2000 patients receiving rapacuronium for intubation during the registration process,[18] Sparr and colleagues[19] reported an 11% incidence of pulmonary side-effects (e.g. bronchospasm, increased airway pressure) after administration of an intubating dose of rapacuronium. Blobner and colleagues[9] subsequently reported an 18% incidence of respiratory complications during intubation with rapacuronium.

After the introduction of rapacuronium into clinical practice, it became apparent that rapacuronium could induce severe (even life-threatening) bronchospasm in children and young adults.[20–22] In the early clinical reports of rapacuronium-associated bronchospasm,[19 23] a majority of the cases occurred in patients with well-known predisposing factors (e.g. asthma, chronic bronchitis, history of smoking). Although it was suggested that histamine or leukotriene release may be responsible for rapacuronium-induced bronchospasm,[5 8] Levy and colleagues[24] failed to find a correlation between plasma histamine levels and the occurrence of bronchospasm.

Recent experiments suggest that the most likely mechanism of rapacuronium-induced bronchospasm may relate to its antagonistic activity at the muscarinic (M_2) receptor (Emala CW, Hirshman CA. A mechanism for bronchospasm induced by rapacuronium: M_2 muscarinic receptor antagonism. *Anesthesiology* 2001; **95**: A1360). On the basis of recent case reports,[20–22] it would appear that another important factor contributing to the occurrence of bronchospasm relates to early stimulation of the airway (e.g. rapid-sequence induction). It has been suggested by Meakin and colleagues[22] that rapacuronium can enhance the increase in pulmonary resistance induced by vagus nerve stimulation by blocking prejunctional M_2 receptors that physiologically inhibit vagally mediated increases in pulmonary resistance. By ensuring an adequate depth of anaesthesia before instrumenting the airway and/or administering a drug which could block the effects of rapacuronium at the M_2 receptor, it might be possible to decrease the risk of bronchospasm in patients receiving rapacuronium for tracheal intubation. Nevertheless, further laboratory and clinical studies would be required to demonstrate that a reliable method exists for preventing bronchospasm before rapacuronium could be considered safe for widespread use by anaesthesia practitioners.

The increasing popularity of the laryngeal mask airway for superficial, 'non-cavitary' surgical procedures has clearly reduced the need for muscle relaxants during ambulatory anaesthesia. However, for brief procedures requiring muscle relaxation without tracheal intubation (e.g. electroconvulsive therapy), rapacuronium was viewed as a potentially useful alternative to succinylcholine in situations where the latter drug was contraindicated.[25] By supplanting the use of intermediate and long-acting NMBAs with shorter-acting muscle relaxants, the risk of residual paralysis after short ambulatory procedures and the attendant morbidity could be reduced. Furthermore, by minimizing the need for reversal agents (e.g. neostigmine, glycopyrrolate), it might be possible to reduce the side-effects related to the use of reversal drugs in the ambulatory setting (e.g. dry mouth, postoperative nausea and vomiting, arrhythmias).

While rapacuronium may provide a faster onset and/or more rapid recovery than other available non-depolarizing NMBAs,[11] the higher cost (per unit dose) and lack of a stable, water-soluble formulation also contributed to its failure to gain widespread acceptance in the anaesthesia community. In assessing the financial consequences associated with the introduction of any new drug, it is important to examine the drug's impact on the total costs of surgical and anesthetic care.[1] Although anesthetic practices have advanced to the point where cost savings from variations in drug use are less important than the cost reductions achieved by system-wide improvements in the efficiency of resource utilization, the pharmacoeconomic impact of rapacuronium was not studied before its introduction into clinical practice.[2] If the introduction of a new non-depolarizing muscle relaxant could facilitate the fast-tracking recovery process after ambulatory surgery and/or potentially reduce recovery care costs, it might well prove to be a cost-effective alternative to a less expensive generic drug (e.g. succinylcholine) in the ambulatory setting.

Conclusions

The failure of rapacuronium to replace succinylcholine, mivacurium and the intermediate-acting muscle relaxants for ambulatory surgery procedures requiring tracheal intubation was related to several factors. Although concerns regarding the occurrence of severe bronchospasm led the manufacturer to withdraw this drug from the US market, unrealistic expectations, such as a 'succinylcholine replacement,' lack of a conveniently administered formulation, the declining use of tracheal intubation in the ambulatory setting, and the failure to demonstrate its cost-effectiveness in clinical practice, were other factors contributing to its failure to gain widespread acceptance in ambulatory anaesthesia. Nevertheless, the availability of a safe and cost-effective fast-onset, short-duration non-depolarizing NMBA would fill a long-standing void in the anaesthetist's armamentarium.

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CLINICAL INVESTIGATIONS

Can molecular similarity-activity models for intravenous general anaesthetics help explain their mechanism of action?

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Background. The importance of molecular shape and electrostatic potential in determining the activities of 11 structurally-diverse i.v. general anaesthetics was investigated using computational chemistry techniques.

Methods. The free plasma anaesthetic concentrations that abolished the response to noxious stimulation were obtained from the literature. The similarities in the molecular shapes and electrostatic potentials of the agents to eltanolone (the most potent anaesthetic agent in the group) were calculated using Carbo indices, and correlated with *in vivo* potency.

Results. The best model obtained was based on the similarities of the anaesthetics to two eltanolone conformers (r^2=0.820). This model correctly predicted the potencies of the R- and S-enantiomers of ketamine, but identified alphaxalone as an outlier. Exclusion of alphaxalone substantially improved the activity correlation (r^2=0.972). A bench mark model based on octanol/water partition coefficients (r^2=0.647) failed to predict the potency order of the ketamine enantiomers.

Conclusions. The results demonstrate that a single activity model can be formulated for chiral and non-chiral i.v. anaesthetic agents using molecular similarity indices.

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The molecular mechanism(s) of i.v. general anaesthesia are unknown. Although a range of putative sites of action have been proposed,[1 2] the molecular properties that determine anaesthetic potency have not been identified. The situation is complicated for the i.v. anaesthetics by their chemical diversity, ranging from simple alcohols to complex steroids, which excludes the possibility of formulating an activity model based on the spatial arrangement of individual atoms or chemical groups.[3] Previous investigations of activity relationships for i.v. general anaesthetics have, therefore, been restricted to either structurally homologous series of compounds (e.g. the steroid anaesthetics),[4–6] or have been based on structurally indiscriminate properties (e.g. their non-polar solubilities).[7]

Computer-modelling techniques have recently been developed that give the *potential* to formulate a single activity model for chemically diverse agents. Such approaches ignore the individual atomic arrangements of the compounds, but consider the three-dimensional molecular properties that are determined by the atomic structure.[8] Such properties include the geometric shapes of the molecules and their electrostatic potentials (a measure of the distribution of charge around the molecule). These molecular properties can be numerically compared by the calculation of similarity indices, and correlated with *in vivo* potencies to formulate activity models.[9] We have previously applied the similarity approach to demonstrate that molecular shape is important in determining the *in vivo* potencies of halogenated ether and ethane volatile anaesthetics.[10]

Preliminary models for i.v. general anaesthetics demonstrate the importance of electrostatic potential in determin-

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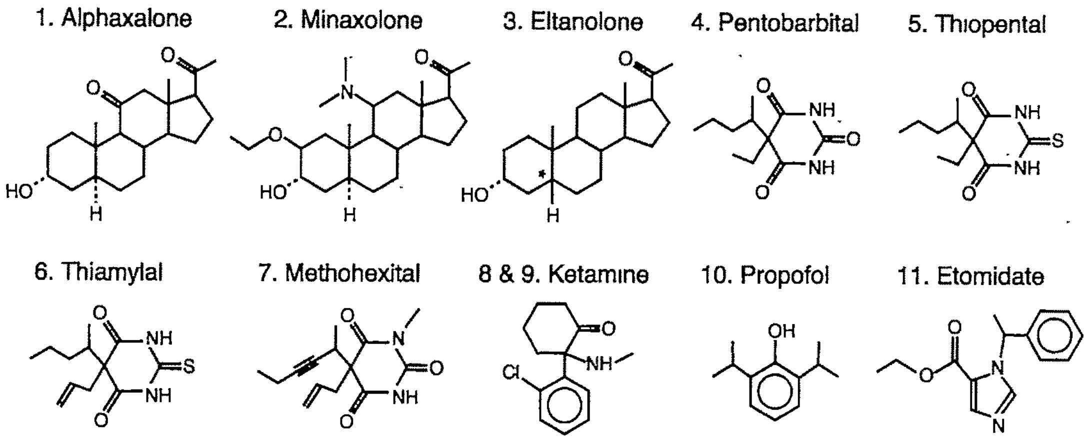

1. Alphaxalone 2. Minaxolone 3. Eltanolone 4. Pentobarbital 5. Thiopental 6. Thiamylal 7. Methohexital 8 & 9. Ketamine 10. Propofol 11. Etomidate

Fig 1 Structural diversity of the i.v. general anaesthetics considered in this study. Note that the hydrogen attached to C5 (*) of eltanolone is in the β configuration (solid line), resulting in a *cis* junction between the A and B rings

ing *in vivo* activity. A model based on electrostatic potential similarity explains 87% of the variance in observed potencies of i.v. general anaesthetics.[11] This represents a substantial improvement compared with a 'conventional' activity model based on the octanol/water partition coefficients of the compounds, which explained only 66% of the variance in observed activity. However, these preliminary investigations did not take into account the effects of chirality of the various agents. The present study is an extension of this earlier work (previously reported to the Anaesthetic Research Society),[11] to develop an improved activity model for the i.v. agents that can address this shortcoming.

Methods

Compounds studied

The structures of the 11 chemically diverse i.v. general anaesthetics considered in this study are shown in Figure 1. The compounds include: the steroid hypnotics, minaxolone (2β-ethoxy, 3α-hydroxy, 11α-dimethylamino, 5α-pregnan 20 one), alphaxalone (5α-pregnan, 3α-hydroxy, 11,20 dione), and eltanolone (5β-pregnanolone); the racemic barbiturates, thiopental, pentobarbital, thiamylal, and methohexital; and a miscellaneous group of propofol, R- and S-ketamine and R-etomidate. Free drug concentrations associated with abolition of the response to a noxious stimulus in 50% of subjects (EC_{50}) were calculated from typical published plasma drug concentration and protein binding data.[12–32] Where possible, potency data were taken from studies where no other adjuvant drugs were administered up to the time of the stimulus (the initial surgical incision in patient studies). However, for alphaxalone (given as Althesin), minaxolone and R-etomidate, concentration-effect data are only available for infusions of the agents in the presence of 67% nitrous oxide. Adjustment has therefore been made assuming the nitrous oxide to represent 0.6 MAC, and the hypnotic drug concentration 0.4 MAC equivalent.

Molecular model construction

Computer-based models of the anaesthetics were constructed using the molecular modelling software SYBYL 6.4 (Tripos Inc, St Louis, USA) on a Silicon Graphics O2 R10000 workstation. All of the compounds were modelled in their un-ionized state. The starting structures were geometry optimized using molecular mechanics minimization, which considers the molecule as a series of spheres (representing the atoms) connected by springs (representing atomic bonds). Potential energy functions, defined in a 'force field', describe the optimum bond lengths, bond angles and torsion angles for the atoms of the molecule. During geometry optimization, the above features are adjusted to minimize the total potential energy of the structure. The default Tripos molecular mechanics force field was used, as implemented in SYBYL 6.4. Gasteiger-Huckel partial charges were assigned to each atom, and non-bonded electrostatic interactions calculated using a distance-dependent dielectric function. The latter simulates the electrostatic screening effect of the solvent, without explicitly including the solvent molecules in the calculations.

Although the i.v. general anaesthetics consist of relatively rigid ring systems, the side chain groups are capable of free rotation. The anaesthetics, therefore, exist as an ensemble of interchangeable configurations, referred to as conformers The lower the potential energy of a conformer, the more frequently that configuration will occur in solution (based on the Boltzmann distribution). This flexibility was considered in our model by deriving a set of low energy conformers for each of the anaesthetics, using a SYBYL random search. In this process, the torsion angles of the molecules are randomly perturbed, and the resultant structures are subjected to molecular mechanics geometry optimization. Only the optimized conformers with a potential energy within +4 kcal mol^{-1} of the lowest energy conformer for a given anaesthetic were retained. The process was repeated until each anaesthetic had been subjected to 10 000 random structure perturbations, or until each of the low energy conformers had been found at least 12 times. A total of 1308 conformers were produced for the 11 anaesthetics at this stage.

The geometries of the 1308 conformers were further refined using quantum mechanics, in which a mathematical description of molecular structure is formed in terms of the nuclei and electron distribution. This provides a more accurate representation of molecular geometry, but is computationally more intensive. The computation time was reduced by using semiempirical quantum mechanics, in which only the valence electrons are considered explicitly and experimentally derived variables are used to represent the nuclei and inner-shell electrons. The geometry optimization was performed *in vacuo* using the MOPAC 6 software package (Quantum Chemistry Program Exchange, Indiana, USA) with the AM1 Hamiltonian. Atomic partial charges were assigned using the Coulson method. After geometry optimization, duplicate conformers (defined as conformers with an RMS difference of <0.2 Å) were removed. The final set consisted of 621 unique conformers for the 11 anaesthetics.

Similarity indices

Alignment of the structurally diverse general anaesthetics was based on the local minimum method,[33 34] in which the structures are aligned so as to maximize their molecular similarity with the conformers of the most active agent in the group. Thus, the anaesthetic conformers were rotated and translated in a SIMPLEX optimization to maximize their similarity with the conformers of eltanolone. Molecular similarity was quantified by the calculation of Carbo indices,[9] which range from 0 (totally dissimilar molecular shapes and electrostatic potentials) to 1 (totally identical). Combined shape and electrostatic potential Carbo indices were calculated using an analytical method[9] with the ASP 3.22 software ('Automated Similarity Package', Accelrys Inc., Cambridge, UK). The conformers of each anaesthetic with the maximum similarity to the eltanolone conformers were retained.

Activity model formulation

Activity models were formulated by correlating the molecular similarity variables with the *in vivo* potencies of the anaesthetics. However, the high co-linearity of the similarity variables prevents the application of standard multiple regression techniques. Hence, the latent variable procedure[35] of partial least squares (PLS) regression was applied, using the PLS Toolbox 2.1.1 (Eigenvector Research, Manson, USA) for MatLab 5 (The MathWorks Inc., Natick, USA). Models using all possible combinations of two similarity variables were considered. In each case, the second similarity variable in the model was orthogonalized to the first using the Gram-Schmidt procedure.[36] This process identifies the information which is common to both variables, and removes this common factor from the second variable, so that the latter contains only 'unique' data (i.e. it is orthogonal to the first variable). The variables were subsequently scaled to mean zero and unit variance, so that they have the same numerical range for the PLS analyses. The number of latent variables included in each PLS model, and the model's predictive capability, were determined by leave-one-out cross-validation.[37] In this process, each model was repeatedly reformulated, but with one of the anaesthetics excluded at each stage. The revised model was used to predict the *in vivo* potency of the excluded agent, and the process repeated until all of the compounds had been excluded once and once only. In effect, cross-validation is testing the ability of the models to predict the activities of an 'unknown' agent. The model with the minimum number of latent variables and best cross-validated r^2 was retained. Confidence intervals (95%) for the final model variables were estimated using bootstrapping[37] over 100 iterations, and statistical significance determined by an analysis of variance (F statistic) using SYBYL.

The possibility of obtaining a chance correlation was tested by randomly re-assigning the observed potency data to different anaesthetics, and repeating the modelling process. A total of 1000 cycles of random perturbations were used, and the mean r^2 and cross-validated r^2 for this distorted data set calculated. For benchmark purposes, a 'conventional' activity model based on non-polar solubility was also formulated for the anaesthetics, using published octanol/water partition coefficients.[38]

Results

Intravenous general anaesthetic potencies

The anaesthetic potencies expressed as plasma drug concentrations associated with no response to a noxious stimulus or surgical incision in 50% of patients (EC_{50}), and octanol/water partition coefficients for the 11 hypnotic agents are summarized in Table 1. These potencies, based on data from the literature, were used for our calculations of equivalent free drug concentrations that abolish a response to the initial surgical stimulus in clinical studies. The potency data were correlated with molecular properties to formulate the anaesthetic activity models.

Octanol/water partition coefficient model

The following bench mark model was obtained using octanol-water partition coefficients (lipophilicity correlation) for the anaesthetic agents (mean variables±95% CI):

Table 1 Non-polar solubilities and typical values for the *in vivo* potencies of the i.v. general anaesthetics considered in this study. †Chiral anaesthetic, potency evaluated using racemate. *Calculated octanol/water partition coefficient. ‡ Octanol/water partition coefficients based on racemate

Anaesthetic	MW	Octanol/water partition coefficient	Total plasma concentration (μg ml^{-1})	Fraction protein bound (%)	Free plasma concentration (μM)	Refs.
Steroids						
1. Alphaxalone	332.5	2.6*	4.8	40	8.662	30–31
2. Minaxolone	405.6	3.7*	1.6	95	0.197	32
3. Eltanolone	318.5	3.97*	3	99	0.094	26–27
Barbiturates						
4. Pentobarbital†	226.3	2.07‡	28	61	48.26	19
5. Thiopental†	242.3	2.59‡	40	85	24.76	12–14, 16
6. Thiamylal†	254.4	3.23‡	26	85	15.33	17–18
7. Methohexital†	262.3	2.4‡	10	75	9.53	15–16
Miscellaneous						
8. R-Ketamine	237.7	2.18‡	4.2	27	12.90	28–29
9. S-Ketamine	237.7	2.18‡	1.4	27	4.30	28–29
10. Propofol	178.3	3.79	14	98	1.57	20–22
11. R-Etomidate	244.3	3.05	1	75	1.02	23–25

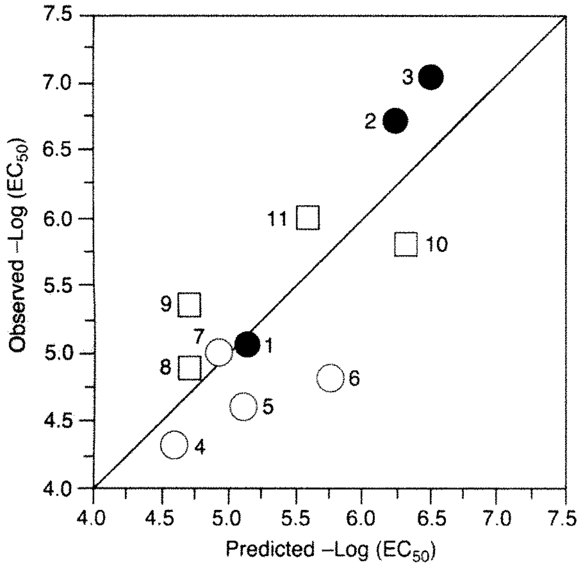

Fig 2 Correlation between observed anaesthetic potencies and values predicted using octanol/water partition coefficients for steroid, barbiturate and miscellaneous i.v. general anaesthetics. Numbers refer to the compounds listed in Table 1. The model explained 64.7% of the variance in the observed activities (P=0.003). Note that the model is unable to predict the different potencies of the enantiomers of ketamine (8 and 9).

$$\text{Predicted} -\log(EC_{50}) = (0.995 \pm 0.043 \times \text{octanol/water partition coeff.}) + 2.535 \pm 0.116$$

This model explained only 64.7% of the variance in the observed activities of the compounds ($F_{(1,9)}$=16.531, P=0.003, n=11). A plot of the predicted anaesthetic potencies (Fig. 2) shows that the model failed to predict the potency order for the enantiomers of the chiral anaesthetic, ketamine. Furthermore, the model had a low predictive power, with a cross-validated r^2 of 0.418.

Molecular similarity-anaesthetic activity models

Models with greater predictive power were obtained using molecular similarity indices. The conformers of each anaesthetic were aligned so as to maximize their molecular similarity to eltanolone, the most active compound in the group. Three eltanolone conformers were identified, which differed in their torsion angles at the $-CO-CH_3$ side-chain attached to the D ring (Fig. 3). The combined shape and electrostatic potential similarities of all the anaesthetics to the individual eltanolone conformers were calculated using Carbo indices. Table 2 lists the maximum similarity values obtained for each anaesthetic. An example of the optimal alignment of the anaesthetics to one of the eltanolone conformers is illustrated in Figure 4. It can be seen that the chemical groups of the i.v. agents are arranged to correspond to the key electrostatic and steric features of the eltanolone conformer.

The best activity correlation was found with a single latent variable model, based on the combined shape and electrostatic potential similarities of the anaesthetics to eltanolone conformers 1 and 2:

$$\text{Predicted} -\log(EC_{50}) = (0.358 \pm 0.024 \times C1) - (0.447 \pm 0.013 \times C2) + 5.377 \pm 0.024$$

where:

C1=Scaled combined similarity to eltanolone conformer 1

C2=Scaled combined similarity to eltanolone conformer 2, orthogonalized to C1

This model explained 82.0% of the variance in the observed activities of the anaesthetics ($F_{(1,9)}$=41.094, P<0.001, n=11). The model was also a good predictor of *in vivo* potency (cross-validated r^2 of 0.755), and correctly predicted the relative activities of the ketamine enantiomers (Fig. 5). However, alphaxalone (the main

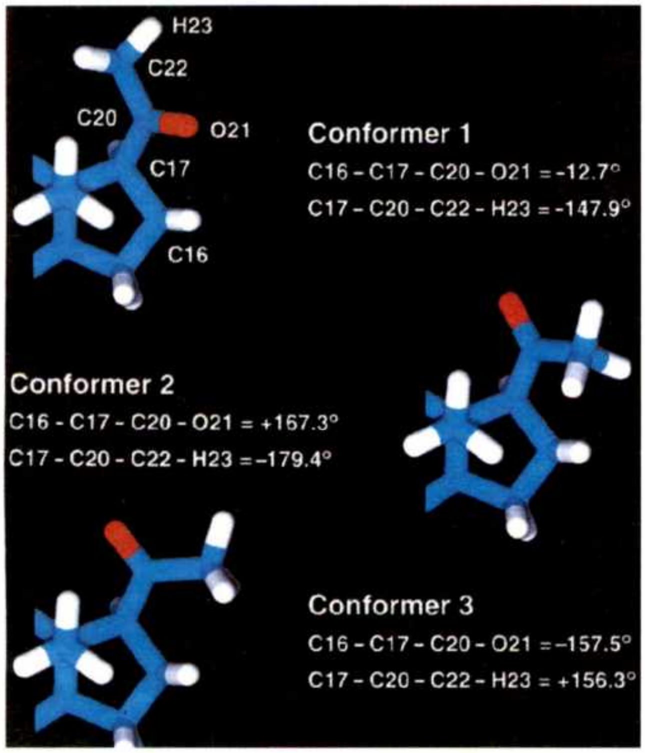
H23
C22
C20
O21
C17
C16
Conformer 1
C16 - C17 - C20 - O21 = -12.7°
C17 - C20 - C22 - H23 = -147.9°
Conformer 2
C16 - C17 - C20 - O21 = +167.3°
C17 - C20 - C22 - H23 = -179.4°
Conformer 3
C16 - C17 - C20 - O21 = -157.5°
C17 - C20 - C22 - H23 = +156.3°

Fig 3 Torsion angles and orientations of the $-CO-CH_3$ side-chain for the three eltanolone conformers identified in this study.

Table 2 Maximum values of Carbo indices describing the combined shape and electrostatic potential similarity of each anaesthetic to the three eltanolone conformers. The data shown were orthogonalized and scaled to mean zero, unit variance for the activity model formulation

Anaesthetic	Eltanolone conformer		
	1	2	3
Alphaxalone	0.880	0.895	0.902
Minaxolone	0.866	0.856	0.872
Eltanolone	1.000	1.000	1.000
Pentobarbital	0.585	0.632	0.628
Thiopental	0.629	0.673	0.671
Thiamylal	0.638	0.655	0.653
Methohexital	0.638	0.670	0.674
R-Ketamine	0.687	0.724	0.714
S-Ketamine	0.693	0.719	0.718
Propofol	0.747	0.740	0.748
R-Etomidate	0.675	0.665	0.686

active component of the steroid Althesin) was identified as an outlier, being less potent than would be predicted from its molecular similarity to the eltanolone conformers.

The influence of the outlier was tested by excluding alphaxalone and repeating the modelling process. A revised single latent variable model obtained, based on the combined shape and electrostatic potential similarities of the agents to eltanolone conformers 2 and 3:

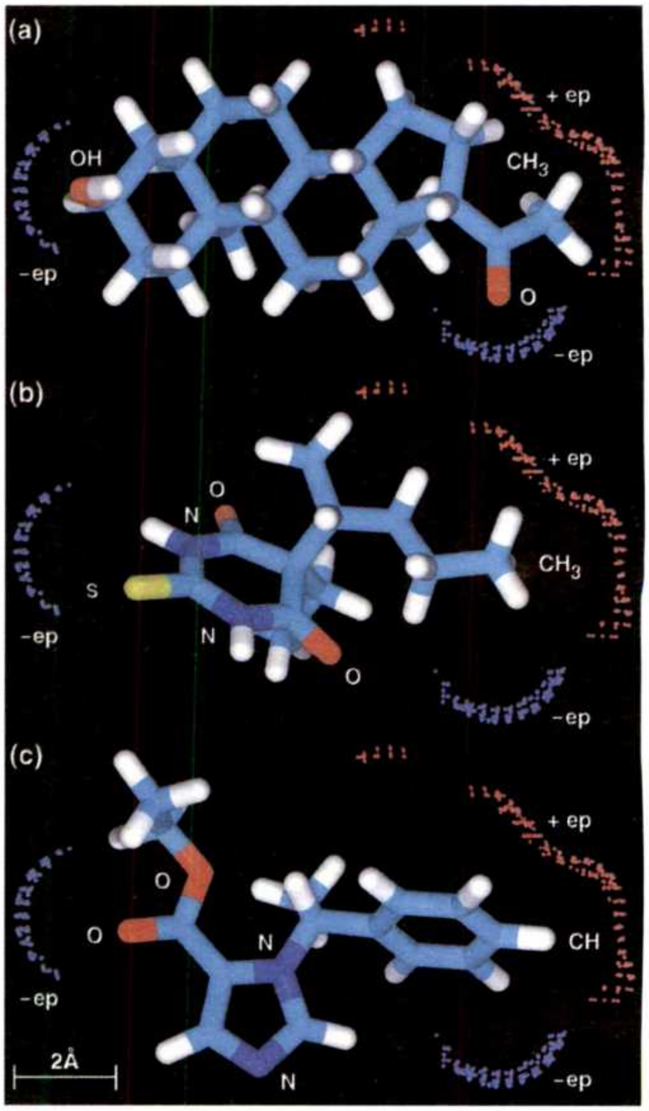

Fig 4 (A) The spatial arrangement electrostatic potential (ep) regions for conformer 2 of eltanolone. Areas of negative potential (<-35 kcal mol^{-1}) are shown as purple spheres, and areas of positive potential ($>+9$ kcal mol^{-1}) as red spheres. The best alignments of thiopental (B) and etomidate (C) that have maximum shape and electrostatic potential similarity to the eltanolone conformer are shown.

$$\text{Predicted } -\log(EC_{50}) = (0.607 \pm 0.047 \times C2) + (0.376 \pm 0.034 \times C3) + 5.392 \pm 0.027$$

where:

C2=Scaled combined similarity to eltanolone conformer 2

C3=Scaled combined similarity to eltanolone conformer 3, orthogonalized to C2

The exclusion of alphaxalone improved the model considerably (Fig. 6), explaining 97.2% of the variance in the observed activities of the compounds ($F_{(1,8)}=278.836$, $P<0.001$, $n=10$). The predictive power of the model was also increased (cross-validated r^2 of 0.950).

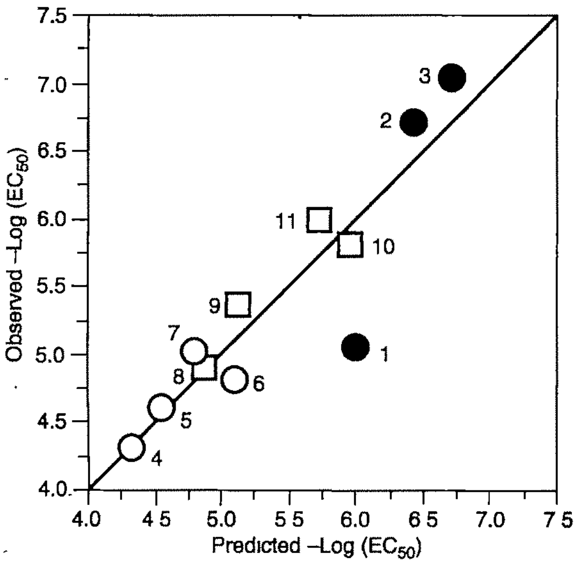

Fig 5 Correlation between observed and predicted potencies using a model based on the combined shape and electrostatic potential similarities of the i.v. agents to eltanolone conformers 1 and 2. The model explains 82.0% of the variance in the observed activities ($P<0.001$), and correctly predicts the potency order of the ketamine enantiomers Note that alphaxalone (1) is an outlier.

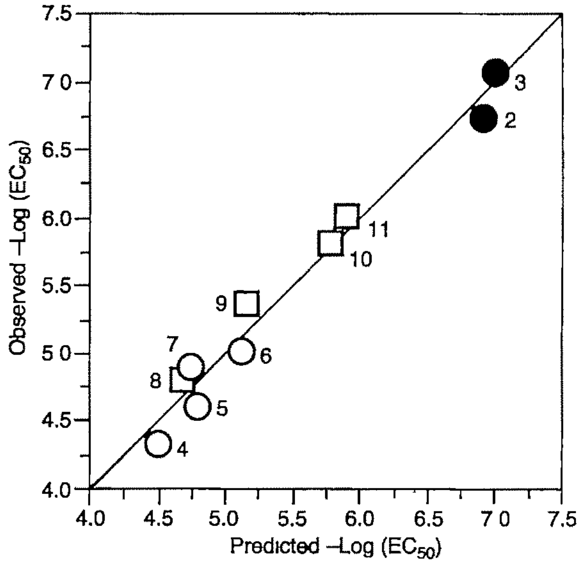

Fig 6 Improved activity model obtained with the exclusion of alphaxalone The model is based on the similarity of the anaesthetics to the electrostatic potentials of eltanolone conformers 2 and 3, and explains 97.2% of the variance in the observed activities of the compounds ($P<0.001$).

Test for chance correlations

The possibility of obtaining chance correlations when using similarity variables was tested by random perturbation of the potency data prior to model formulation. With alphaxalone included, the mean r^2 (±95% CI) of the best models over 1000 perturbations was only 0.202±0.011. The standard deviation of the r^2 values was 0.169. Unlike the true activity data set, exclusion of alphaxalone did not improve the correlation. Furthermore, the molecular similarity models were very poor predictors of *in vivo* potency after random perturbation of the activity values, with a mean cross-validated r^2 of −0.662±0.036 (n=1000) and standard deviation of 0.584.

Discussion

The results of this study indicate that a common activity model can be formulated for chemically diverse i.v. general anaesthetics, based solely on their similarities in geometric shape and electrostatic potential. Whilst previous similarity studies have demonstrated the importance of these molecular properties in determining the anaesthetic activities of structurally homologous inhalational agents,[10] the activity model presented here represents the first similarity model for structurally diverse chiral and non-chiral i.v. anaesthetics. Furthermore, the similarity model is more effective at predicting *in vivo* potencies than a model based on octanol/water partition coefficients, which do not provide an adequate physico-chemical correlate for i.v. general anaesthetic activity.

There are several factors that could influence the effectiveness of our activity model. One of the key factors is the EC$_{50}$ calculations of *in vivo* anaesthetic potency. The endpoint used in this paper for the potency of Althesin (as alphaxalone), minaxolone, methohexital, thiopental, propofol, eltanolone, R-etomidate and the isomers of ketamine has been the plasma drug concentration during infusion anaesthesia associated with suppression of a noxious stimulus (initial surgical incision) in 50% patients (or the equivalent endpoint in animals). The data shown in Table 1 are typical values of the derived kinetic variables. For pentobarbital and thiamylal, the concentration values cited are the best approximation to those in the blood at the time of the surgical incision following single bolus doses to patients. Because of the long elimination half-lives of these barbiturates, the decline in the plasma drug concentration (and hence the brain concentration) will be slow after the initial redistribution phase, and we have therefore assumed that pseudo-steady state conditions exist. However, the potency of an i.v. anaesthetic is related to its brain:effect-site concentration rather than the plasma concentration. Based on the known kinetics of our 11 hypnotic agents and their blood:brain uptake times, we have assumed that for all agents there is approximate blood:brain equilibration.

The effects of stereochemistry on hypnotic potency have been described for the isomers of etomidate,[39 40] the barbiturates,[41] ketamine,[42 43] and some of the steroid anaesthetics.[44–46] In the case of ketamine, there are kinetic and dynamic data available for both enantiomers as well as the racemate.[42 43 47] Although there are comparative data for the dynamics of the two enantiomers following i.v. bolus dosing,[48] there are fewer data for infusions of ketamine and none for the R(–) isomer. Clinical studies with infusions of ketamine show the anaesthetic potency of the S(+) enantiomer to be twice that of the racemate,[48] with the potency ratio for S(+) to R(–) being 3 to 4:1.[43] Based on the infusion data of Adams and colleagues[48] and Idvall and colleagues,[49] we have assumed the Cp_{50} (plasma drug concentration associated with no response in 50% of patients receiving ketamine alone) for racemic ketamine to be 2.5 to 3.0 $\mu g\ ml^{-1}$, the S(+) isomer 1.4 $\mu g\ ml^{-1}$, and hence the R(–) isomer 4.2 $\mu g\ ml^{-1}$. Differences in potency have been demonstrated *in vitro* for the stereoisomers of etomidate [39], but *in vivo* only the R(+) isomer is present in the clinically available formulation.

There are, however, no mammalian data examining the dynamics of the various enantiomers of the barbiturates, although stereo-kinetics have been determined for several of the drugs (particularly thiopental, pentobarbital and thiamylal) which reveal subtle and possibly important differences in disposition which might affect the concentration–effect relationships for different enantiomers.[50–52] We have, therefore, based our potency calculations for the barbiturates on racemate concentrations.

It is difficult to offer firm reasons for alphaxalone being an outlier in our similarity model. Alphaxalone is the major hypnotic steroid in Althesin, with alphadolone acetate being present to increase lipid solubility. Richards and White[53] showed additivity between alphaxalone and alphadolone in rodents; but there are no comparable data for man. Our studies to determine the 'anaesthetic or immobilizing' concentration of Althesin only measured plasma alphaxalone concentrations.[30] However, when the kinetics of the two steroids are studied, the observed plasma concentrations show the expected 3:1 concentration ratio with similar disposition profiles.[54] The only available reported estimate for alphaxalone plasma protein binding is 40%.[31] This binding estimate appears to be low and not in keeping with other pregnane steroids, where plasma protein binding is often concentration dependent, and of the order of 55–80%. This may be one cause for our apparent over-estimation of the observed plasma EC_{50} free drug concentration. There are no published concentration–effect data for Althesin under steady state conditions in other mammalian species to validate this observed concentration–effect relationship.

What does this study indicate about the mechanism of anaesthetic action? The fact that a common activity model can be formulated for structurally diverse i.v. general anaesthetics suggests two features.

(i) First, that there is a common molecular basis for the mechanism of general anaesthesia. This does not necessarily imply that there is a common site of action: indeed, *in vitro* studies indicate that $GABA_A$, neuronal nicotinic acetylcholine and NMDA receptors are all sensitive to the wide range of i.v. anaesthetic agents at clinically relevant concentrations,[1 55 56] although the involvement of these ligand-gated ion channels in inducing general anaesthesia *in vivo* is less clear.[57 58] Rather, our studies suggest that certain molecular features involved in determining anaesthetic activity are common to all the 11 hypnotic agents.

(ii) Second, that molecular shape and electrostatic potential are key in determining the *in vivo* potencies of chiral and non-chiral i.v. general anaesthetics. This opens the possibility of deriving a non-structural 'pharmacophore' for general anaesthetics, based on their three-dimensional steric and electrostatic features.

Whether the molecular shape characteristics *in silico* of a novel putative hypnotic agent can be used to predict its subsequent *in vivo* potency remains to be determined. However, identification of a three-dimensional pharmacophore will clearly be the first stage in this process.

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Model-based administration of inhalation anaesthesia. 4. Applying the system model

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Background. We developed and tested a simple dosing strategy for rapid induction with isoflurane followed by maintenance under minimal-flow conditions, that is 0.5 litre min^{-1} total fresh gas flow (FGF). An end-expired concentration was to be achieved within 5 min in a desired therapeutic window, that is 0.8–1.1 vol%, and to be maintained within it for at least 30 min.

Methods. With our new model we computed a three-stage regimen using one fixed vaporizer setting: 3 vol% isoflurane in a FGF of 3 and 1.5 litre min^{-1}, each for 3 min, and 0.5 litre min^{-1} thereafter. The ratio of nitrous oxide:oxygen was, consecutively, 2:1, 2:1, and 2:3. We evaluated this scheme in 58 adult patients (body mass 74 (SD 13) kg), mostly during eye and ear, nose, and throat surgery.

Results. Measured oxygen (33–45 vol%) and nitrous oxide concentrations (66–50 vol%) evolved in accordance with those computed. In five patients with a median of body mass 92 kg (range 76–126 kg), inspired oxygen concentrations decreased to less than 30 vol%. End-expired isoflurane concentration entered the window after 2 min (range 1.0–5.67 min) and attained its maximum, that is 0.96 vol% (0.8–1.2 vol%), after 3.45 min (1.67–6.33 min). The mean end-expired concentration was in the desired window from 3–60 min and an average of 72% of individual measurements were within the window from 3–30 min. The scheme was adapted in six patients (excluded from analysis) because of hypotension.

Conclusion. The regimen is easily remembered, reliable, and lends itself to alternative strategies, but must be guided by the monitoring of gas and vapour concentrations and haemodynamic variables.

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The technique of low-flow anaesthesia (≤1 litre min^{-1} total fresh gas flow (FGF)) is a dichotomy. On the one hand, this technique offers many advantages; on the other, it is poorly accepted. For example, it is recognized that it is very economical and reduces environmental pollution. Technical barriers no longer exist as modern anaesthesia systems integrate all the necessary equipment to facilitate safe administration. Nevertheless, low-flow techniques are still not universally used in current clinical practice. A major problem is the lack of a simple dosing strategy that aids in attaining and maintaining pre-defined concentrations of the inhaled anaesthetics.

Our principal aim was to develop such a dosing strategy capable of achieving low-flow conditions in a few minutes and able to work within the time constraints of a routine session. Thus, the desired concentration of an inhaled anaesthetic had to be attained rapidly, as anaesthesia should be adequate early in the operation, and with a minimum of manual interventions. Also, the dosing regimen had to be simple enough to be easily remembered and easily applied without any calculations.

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Table 1 Sequences of FGF and vaporizer settings in the three isoflurane dosing schemes (A–C) tested by computer simulation. The pre-scheme gas flows were 9–12 litre min^{-1} air (3 min), 5 litre min^{-1} each of nitrous oxide and oxygen (2 min), and 6 litre min^{-1} nitrous oxide in 3 litre min^{-1} oxygen (5 min)

Stage	Time (min)	FGF oxygen (litre min^{-1})	FGF nitrous oxide (litre min^{-1})	Vaporizer setting (vol%)
Scheme A				
1	0	0.5	0.5	5
2	5	0.5	0.5	3.5
3	10	0.5	0.5	2.5
4	15	0.5	0.5	2
Scheme B				
1	0	0.5	0.5	5
2	5	0.5	0.5	3.5
3	10	0.5	0.5	2.5
4	15	0.3	0.2	2.5
Scheme C				
1	0	1	2	3
2	3	0.5	1	3
3	6	0.3	0.2	3

Table 2 Physical characteristics of model subjects. Simulations are for three typical patients: a S(mall) older, a M(edium), and a L(arge) young patient. A full characterization of patient M was given elsewhere, as well as the dependence of physiological variables, e.g. functional residual capacity and cardiac output, upon the tabulated data[1]

	S	M	L
Body mass (kg)	55.0	70.0	95.0
Height (m)	1.65	1.80	1.95
Age (yr)	60	40	20
Sex	Female	Male	Male

Devising a suitable regimen in the clinical environment might prove to be difficult or even dangerous to patients. Therefore, we applied version 2 of our system model, recently developed and validated for desflurane.[1–3] We now present: (i) the theoretical testing of potentially useful dosing strategies through different 'what happens if' scenarios; (ii) the clinical validation of a mnemonic (easily remembered) sequence of vaporizer settings and flows for isoflurane in a mixture of nitrous oxide and oxygen.

Patients and methods

The study proceeded in two steps: a computer study was followed by clinical testing.

Computer study

The dosing strategies tested were based on our practical experience with various low-flow techniques. Minimum requirements were that the end-expired isoflurane concentration would: (i) enter a therapeutic window of 0.8–1.1 vol% within 5 min; (ii) remain within that window for at least 30 min under low-flow (total FGF $\leq$1 litre min^{-1}) and preferably 'minimal-flow'[4] conditions (total FGF=0.5 litre min^{-1}).

Of all schemes tested, only three (A–C) will be illustrated. They have to be judged against the minimum requirements as well as additional practical and theoretical arguments. These schemes and the pre-scheme gas flows are given in Table 1. Zero time is the start of the administration of isoflurane.

Scheme A is a four-stage scheme using the maximum vaporizer setting to hasten induction with a FGF of 1 litre min^{-1}. Only the vaporizer setting is adjusted during the course of the anaesthetic.

Scheme B, being a variant of A, eventually uses minimal-flow conditions and therefore necessarily uses 2.5 vol% isoflurane and not 2 vol% as A. In scheme B both the vaporizer and Rotameter settings must be adjusted.

Scheme C is a three-stage scheme starting with a relatively high flow of fresh gas for a very short period. The vaporizer setting remains the same throughout the anaesthetic. Only the FGF is adjusted. The scheme starts with three times the number 'three': 3 vol% isoflurane in 3 litre min^{-1} fresh gas for 3 min. After the first 3 min the FGF is halved. After another 3-min period, the FGF is reduced to the preferred minimal-flow conditions. All three schemes satisfied our minimum requirements ((i) and (ii) above), but scheme C was selected for clinical testing because it appeared to be simple as well as mnemonic.

Simulations with scheme C were performed for three typical patients of different body sizes and age (Table 2), aiming at an 'ideal' alveolar carbon dioxide tension of 5.33 kPa. End-expired concentrations of gas species were calculated as described elsewhere.[3] Nitrous oxide concentrations were averaged over the respiratory cycle (=the sum of one-third of the inspired and two-thirds of the end-expired concentration (I:E ratio=1:2)) to match measured nitrous oxide concentrations (*vide infra*).

Clinical study

Anaesthetic management

Seventy-eight consenting patients (ASA Physical Status I–II; age 17–69 yr) were studied after approval of the Institutional Ethics and Research Committee. They were to undergo elective surgical procedures expected to last at least 45 min and to cause negligible blood loss (eye or maxillofacial surgery, mostly ear, nose, and throat (ENT), and one patient for lumbar laminectomy). Oxazepam 10–30 mg was given orally 1 h before surgery. An intravenous (i.v.) catheter was inserted and basic monitoring (ECG, non-invasive arterial pressure (NIBP), heart rate, arterial saturation by pulse oximetry) established. Arterial pressure was measured with a 1-min interval for 60 min, a 3- to 5-min interval thereafter, and whenever judged necessary by the attending anaesthetist (R.V.).

Anaesthesia was induced with fentanyl 0.1–0.2 mg i.v. and a dose of thiopental sufficient to obtund the eyelash reflex, followed by vecuronium or rocuronium. The patient's lungs were ventilated manually by mask for 2–3 min using a FGF of 10 litre min^{-1} (nitrous oxide:oxygen, 1:1 ratio). Following tracheal intubation with a cuffed tube, the patient's lungs were artificially ventilated with a high FGF of 9 litre min^{-1} (nitrous oxide:oxygen, 2:1) for 5–10 min. Additional doses of i.v. anaesthetic were given as judged appropriate. Prophylactic antiemetic therapy was given at the discretion of the attending anaesthetist (metoclopramide 10 mg or/and droperidol 1.25–2.5 mg i.v.).

Following the period with high FGF, scheme C was applied (Table 1). The timer of the anaesthesia system was used to measure the time periods. During maintenance we did not modify the isoflurane administration unless the patient's responses required so (*vide infra*). We therefore monitored the response of the patient to surgery by the assessment of NIBP, heart rate, and heart rate variability judged by ear with the aid of pulse oximetry, as well as the end-expired isoflurane concentration. Extra fentanyl (increments of 0.05–0.1 mg) was given intravenously according to clinical needs. The lungs were ventilated with a ventilatory frequency of 10–12 bpm (I:E ratio of 1:2) and a tidal volume sufficient to maintain the end-expired carbon dioxide tension at 3.7–4.7 kPa.

Equipment

The anaesthetic equipment consisted of the Modulus CD anaesthesia system (Ohmeda, Madison, USA) as routinely used in our operating theatres for eye, ENT, and neurosurgery. An ARKIVE automated anaesthesia record-keeper provided a computerized anaesthetic record of patient's vital signs. All monitored data were saved on a floppy disk drive integrated in the anaesthesia system.

The anaesthetic breathing system comprised a soda-lime canister (part of the Ohmeda GMS (Gas Management System) Absorber), two 1-m corrugated tubes in each limb, a water trap in each limb, and a Y-piece. A switch in the GMS allows swift alternation between reservoir bag and ventilator. A 2-litre bag at the end of 1-m length of corrugated tubing was used for spontaneous breathing and manual ventilation by mask. A standing bellows ventilator (Ohmeda 7850) supported artificial ventilation of the lungs. A scheme of the breathing system with an internal volume of 6.6 litre, as used during artificial ventilation, is given elsewhere.[1] Leaks in the circuit were detected by plugging the Y-piece, pressurizing the breathing system to 4 kPa, and observing the volume and pressure gauge; a gas leak up to 60 ml min^{-1} was accepted.

The integrated infrared multi gas monitor sampled gas from a point between the Y-piece and the tracheal tube to assess inspired and end-expired carbon dioxide and isoflurane concentrations, as well as nitrous oxide concentrations averaged over the whole respiratory cycle. The analyser was calibrated once per day with room air and a canister of gas provided by the manufacturer. We verified the calibration for isoflurane with a calibration gas mixture containing 1 vol% isoflurane in 30 vol% oxygen, 30 vol% nitrous oxide, and balance gas nitrogen (AGA Gas, The Netherlands). Sample gases (150–230 ml min^{-1}) were redirected to the breathing system, as well as the reference room air taken by the analyser to calibrate its zero baseline at preset intervals (three times during the first hour after switching on the anaesthesia system, and every hour thereafter; calibration lasts 15 s).

Oxygen was measured with the integrated fuel cell, calibrated with room air. The accuracy of the Rotameters was checked against a bubble flow meter. Isoflurane was delivered to all patients by the same Ohmeda Tec 5 vaporizer.

Data handling

From the variables saved on floppy disk the following were analysed: inspiratory oxygen and averaged nitrous oxide concentrations (rounded to whole percentages), inspiratory and end-expired isoflurane concentrations (rounded to one decimal), heart rate, and NIBP (systolic (SAP) and diastolic (DAP) arterial pressure). Basically, gas and vapour concentrations were studied at 20 s, heart rate and NIBP at 1-min intervals. This basic scheme could not be applied throughout because the study data were saved in two different ways, as a result of an unavoidable upgrading of the system software in the course of the study.

The old software saved all variables, except NIBP, at 20-s intervals, for example at 0, 20, 40, 60, 80, 100 s, etc. After each measurement of the NIBP, all variables, including NIBP, were saved in addition to the basic 20-s scheme, for example at 12 and 72 s. These additional values for variables other than NIBP were discarded. The time points at which NIBP was measured were always rounded to whole minute.

With the new software, saving NIBP data interrupted the basic 20-s scheme. Thus, no values were available at the 20-s interval nearest the time point where NIBP was saved. In our example, no data would be saved at 20 and 80 s. This led to 'missing values'. The values for the gases and vapours saved along with the NIBP could not be used because rounding off to the nearest time point would have distorted the time course of the gas and vapour concentrations.

Haemodynamic variables

To evaluate the haemodynamic effects of using scheme C, we assessed the variation with time of arterial pressure and heart rate. The last values obtained before the administration of isoflurane were judged adequate by the attending anaesthetist (R.V.) and used as reference values. The haemodynamic variables were studied until the isoflurane administration was discontinued.

Bradycardia (heart rate <40 beats min^{-1} for at least 30 s) caused by the oculocardiac reflex was treated with 0.5 mg atropine i.v. and by releasing traction on extraocular muscles. Hypotension was defined as SAP less than 80 mm Hg for at least 2 min. For middle ear surgery, parotidectomy, and dacryocystorhinostomy, hypotension was defined as a SAP less than 70 mm Hg for at least 3 min because a reduction in arterial pressure was used to provide good operating conditions. Hypotension was initially treated with i.v. replacement therapy. Hypotension lasting longer than 5 min was treated by reduction of the end-expired isoflurane concentration. The time was noted when this occurred and these patients were excluded from analysis.

Performance indicators

To assess the performance of scheme C, we identified the point count (PC). This is the percentage of measured end-expired isoflurane values below, within, and above the therapeutic window of 0.8–1.1 vol% for each 3-min interval of the first 30 min after the introduction of isoflurane. Note that the values 0.8 and 1.1 vol% belong to the window.

PC was calculated for: (i) pooled data from all patients; and (ii) each patient. From the latter PC, we assessed the number of those patients for whom *all* end-tidal isoflurane concentrations, observed in a 3-min period, were below, within, or above the window, and of those with concentrations crossing the 0.8 or 1.1 vol% limit.

A detailed analysis of the first 7 min of the anaesthetic, that is the initial phase of isoflurane wash-in, was performed to detect: (i) onset time (t_{onset}), that is the time needed to attain the therapeutic window; (ii) C_{max}, that is the maximum end-expired concentration; and (iii) t_{max}, that is the time needed to attain C_{max}.

Regression analysis

A regression line of end-expired isoflurane concentrations against time (from 15–60 min) was calculated for: (i) scheme C in patient M; and (ii) each of the patients retained in the clinical study. The individual estimated slopes were averaged over the patients and reported as mean (SD) and 95% confidence interval (CI).

Results

Computer study

Figure 1 illustrates selected computed results. For three typical patients, the complete time courses of the oxygen and nitrous oxide concentrations only differed slightly across the different schemes (not shown). For the same scheme, however, there are clinically important differences between model patients. This is illustrated for scheme C in Figure 1 (upper). Under low-flow or minimal-flow conditions (6–60 min), the inspiratory concentrations of oxygen evolve approximately between 30 and 45 vol% for the standard patient M, and the averaged concentrations of nitrous oxide between 65 and 55 vol%.

In patient M, schemes A and B cause the end-tidal isoflurane concentration to enter the therapeutic window after 4 min and to stay within the window until 60 min (Fig. 1, lower). As a result of scheme A, the isoflurane concentration stays in the middle half from 4 to 60 min. As a result of C, the isoflurane concentration enters the window after 2 min, stays within it until 60 min, and even travels in the middle half from 2.5 to 60 min, except for the period 9–24 min. The regression line (15–60 min) has an intercept of 0.78 vol% and a positive slope of 0.0042 vol% min^{-1}.

In patients S and L, however, scheme C causes the end-expired isoflurane concentration to enter the therapeutic window after 1.5 and 2.5 min, respectively, and results in an overshoot (>40 min) or undershoot (7–40 min), respectively.

The three schemes do not differ grossly as to the product of the duration of administration of isoflurane and the sum of the end-expired concentrations of nitrous oxide and isoflurane, expressed as multiples of MAC: 1.3, 1.22, and 1.3 MAC×hours for schemes A, B, and C (patient M), respectively. The calculated usage of liquid isoflurane for schemes A, B, and C in 60 min is 7.4, 5.7, and 6.2 ml, respectively. The relatively high flow in C needed for rapid induction results in a usage 9% greater than that of B.

Clinical study

The results are based on data from 58 patients because the data from 20 were discarded for three reasons: technical failures (eight), duration of isoflurane administration for less than 30 min (six), hypotension (five), and both hypotension and duration for less than 30 min (one). If hypotension occurred, it was always within 30 min of the start of isoflurane administration.

The characteristics of the average patient in the study (Table 3) are in reasonable agreement with those of our model subject (patient M; Table 2). One male patient may be designated an outlier because of his body mass index which was 35.6 kg m^{-2}. Recovery from the anaesthetic was uneventful in all patients.

The average measured oxygen and nitrous oxide concentrations (Fig. 2) were in close agreement with those predicted for patient M. Oxygen concentrations slowly increased from approximately 33 to 45 vol%, whereas nitrous oxide concentrations slowly decreased from approximately 66 to 50 vol%. In five patients with 92 kg as median body mass (range 76–126 kg), inspired oxygen concentrations decreased to less than 30 vol%. The number of patients still anaesthetized became progressively fewer after 30 min. Most results from the clinical study were limited to the first 60 min of anaesthesia because after 60 min the number of patients became less than 30 (Fig. 2).

Figure 3 shows that, between the 15 and 60 min, there was a slight positive drift in the inspired concentration of isoflurane from approximately 1.1 to 1.2 vol%. The ratio of inspired concentration to vaporizer setting was approximately 1:3 for 7–60 min. The group slope of the regression lines of end-expired isoflurane against time (15–60 min)—

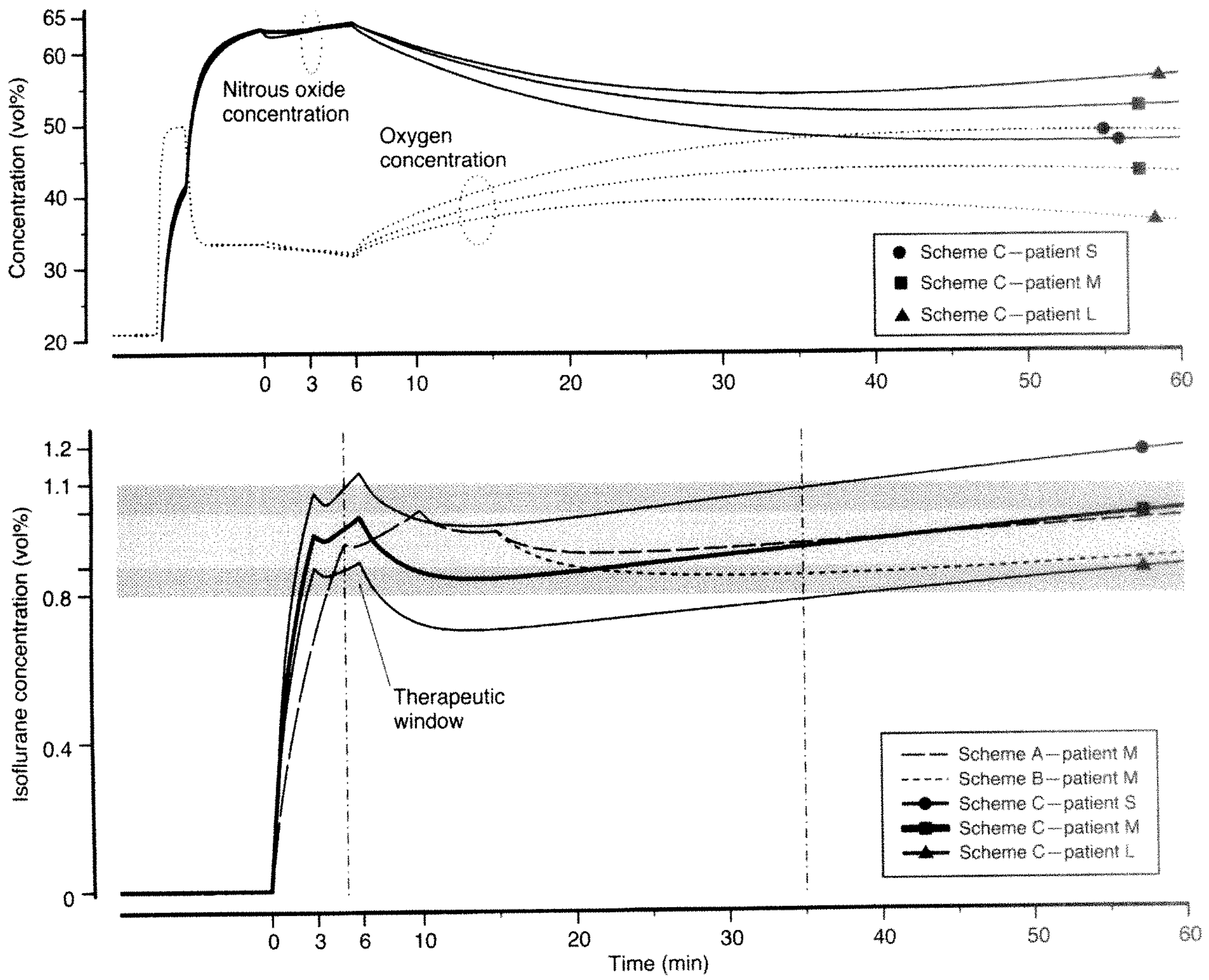

Fig 1 Selected simulations resulting from schemes A, B, or C (Table 1) for three typical patients of different body size and age (Table 2). (Upper) Inspired oxygen and averaged nitrous oxide concentrations plotted against time, as a result of applying scheme C, for a small (S), medium (M), or large (L) patient. (Lower) End-expired isoflurane concentrations resulting from schemes A and B for a medium patient, and from scheme C for a small, medium, and large patient. Time 0=time point at which isoflurane is introduced. The shaded areas mark the therapeutic window (0.8–1.1 vol%; grey) and its middle half (0.875–1.025 vol%; light grey). The aim was that end-expired isoflurane concentrations would enter the desired window in less than 5 min and would stay within that window for at least 30 min. The vertical lines mark 5 and 35 min after the start of isoflurane administration.

Table 3 Patient data. e=eye, m=maxillofacial (mostly ENT), l=lumbar laminectomy. BMI=body mass index (patients with a BMI <20 kg m^{-2} are considered slender; patients with a BMI >25 kg m^{-2} are designated obese)

	Sex (M/F)	**ASA grade (I/II)**	**Age (yr)**	**Body mass (kg)**	**Height (m)**	**BMI (kg m^{-2})**	**Surgery (e/m/l)**
N	34/24	33/25					38/19/1
Mean (SD)			42 (16)	74 (13)	1.73 (0.11)	24.95 (3.07)	
Range			17–69	54–126	1.52–1.96	18–35.6	

averaged over 58 patients—was 0.0035 (0.0024) vol% min^{-1} with a 95% CI from 0.0028 to 0.0041 vol% min^{-1}.

Table 4 shows PCs from pooled data obtained after applying dosing strategy C. Within 6 min, the PC within the window was greater than 90%, then decreased to stabilize at around 66%, and eventually scored 75% at 30 min.

Figures 4–6 focus on the individual curves, especially in the early phases. Scheme C satisfied our requirements for the majority of patients. From 3–30 min, 60–83% of the patients remained fully within the predetermined window (Fig. 4). Almost all patients were crossing the lower limit in the first period (0–3 min), and patients suffering from overshoot were virtually absent (Fig. 4). The average onset time t_{onset} was approximately 2 min, and for all but three patients $t_{\text{onset}} \leq 3$ min (range 1.0–5.67 min) (Fig. 5). Figure 6 gives the plot of peak isoflurane concentrations against the

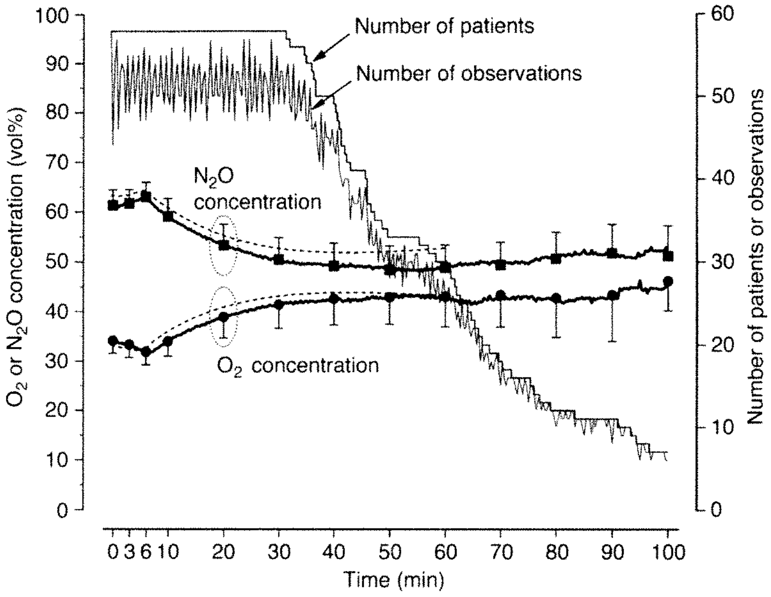

Fig 2 Observed and model predicted results for oxygen and nitrous oxide after applying scheme C The inspiratory oxygen and averaged nitrous oxide concentrations (left *y*-axis) are shown along with the number of patients still anaesthetized (step plot) and the number of observations (line plot; right *y*-axis). The differences between these two numbers result from missing values. The continuous heavy lines represent the means of the measured concentrations. The spread of data is reflected by 1 SD in the positive (nitrous oxide) or negative direction (oxygen) at time 0, 3, 6, 10 min, and at 10-min intervals thereafter. Predicted curves (dashed lines) are included for nitrous oxide and oxygen. Time zero is the start of isoflurane administration. Reductions of FGF occur at 3 and 6 min (Table 1). At the later times (>60 min) the mean becomes more erratic because the number of observations becomes progressively fewer.

time the maximum occurs. The maximum concentration was attained within 3 min in 38, and within 6 min in 56 out of 58 patients. t_{max} averaged 3.45 min (range 1.67–6.33 min), whereas C_{max} averaged 0.96 vol% (range 0.8–1.2 vol%). Observations that fell outside the therapeutic window were mostly 'too low'—with isoflurane concentrations always ⩾0.6 vol% (Fig. 4).

Figure 7 illustrates the haemodynamic variables against time. Reference values (mean (SD)) for SAP, DAP, and heart rate were 121 (25) mm Hg, 72 (14) mm Hg, and 75 (14) beats min^{-1}, respectively. Initially SAP and DAP decreased sharply to 109 (19) and 63 (11) mm Hg, respectively, and from 6 min onwards they showed a slow negative drift of 0.18 (P<0.001) and 0.11 mm Hg min^{-1} (P<0.001), respectively. Atropine was given to 14 patients.

Discussion

The main objective of the present study was to develop and to test a dosing strategy for the rapid induction of a low-flow isoflurane anaesthetic in order to improve clinical conditions during the first 30 min of anaesthesia. Although there are proposals in the literature for the maintenance of anaesthesia, there is only one report describing strategies to rapidly achieve and maintain a predetermined level of anaesthetic under low-flow conditions.[5] No experimental validation was performed, however, and only the administration of inhalation anaesthetics in oxygen was studied.[5]

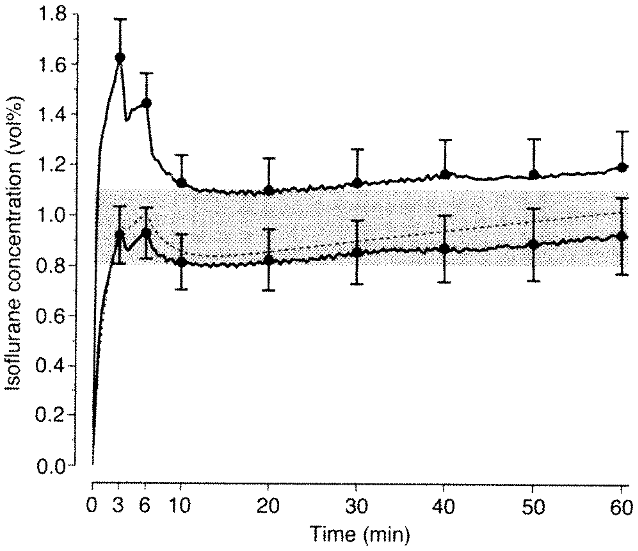

Fig 3 Observed results for isoflurane after applying scheme C. The continuous lines represent the means of the inspiratory and end-expired isoflurane concentrations. The spread of data is reflected by 1 SD in the positive direction (inspiratory concentration) or in the positive and negative directions (end-expired concentration) at 3, 6, and 10 min, as well as at 10-min intervals thereafter. The curve predicted for patient M is included for end-expired isoflurane (dashed line). Time zero is the start of isoflurane administration. Reductions of FGF occur at 3 and 6 min (Table 1). The shaded area marks the therapeutic window (0.8–1.1 vol%).

Table 4 Performance analysis for scheme C (Table 1) based on PCs from pooled data. There were 461 to 518 measuring points per 3-min period. PCs are percentages of measuring points below, within, and above the therapeutic window, i.e. 0.8–1.1 vol% end-expired isoflurane concentration, for each 3-min period

Period (min)	'Too low' (<0.8 vol%) (%)	Within window (≥0.8 vol% and ≤1.1 vol%) (%)	'Too high' (>1.1 vol%) (%)
0–3	64.4	35.6	0.0
3–6	5.8	94.0	0.2
6–9	13.6	86.4	0.0
9–12	27.7	72.3	0.0
12–15	36.9	63.1	0.0
15–18	37.5	62.5	0.0
18–21	36.3	63.7	0.0
21–24	34.1	65.9	0.0
24–27	30.0	69.6	0.4
27–30	24.1	74.5	1.4

We realized that if the scheme was to have practical value it had to be appealing, attractively simple, easily remembered, and yet effective. As long as the average clinical anaesthetist does not have access to a computer-controlled system and must resort to manual adjustment of the vaporizer and Rotameters, any dosing strategy adds to their array of tasks. Complex dosing schedules derived from a model may, therefore, receive low priority compared with direct patient care. A practical dosing scheme should offer a balance between feasibility, reliability, and the potential for economic savings.

Our criteria were translated into the following specific requirements. The end-expired isoflurane concentration should enter the desired therapeutic window, 0.8–1.1 vol%, in less than 5 min and should stay within that window for at least 30 min under minimal-flow conditions. The total number of adjustments of the vaporizer and Rotameters should be minimal. The time period during which adjustments have to be made should be short. If these requirements are met, the anaesthetist can focus on the patient during a busy anaesthetic and yet rely upon the effectiveness and reliability of the dosing strategy.

Scheme C proved to match our requirements: reliable wash-in was obtained by setting the vaporizer once (the vaporizer is turned to the chosen setting, and is then left unaltered throughout the operation) and the Rotameters three times within a 6-min period. After 3 min the average end-expired concentration was a little over 0.9 vol% (Fig. 3); individual measurements fell outside the pre-defined window but, from 3 min onwards, at least 63% were within the window with almost all the remainder falling below it (Table 4).

In Figure 3 (10–20 min), the mean measured isoflurane concentration is close to 0.8 vol%, which superficially suggests that 50% of individual measurements should be 'low', against the 28–38% in Table 4. However, as the infrared analyser reads only to the nearest 0.1 vol%, a

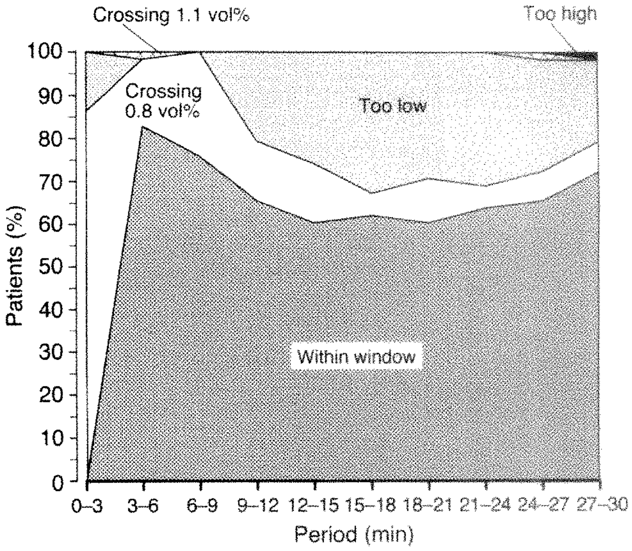

Fig 4 Performance of scheme C for the first 30 min. Numbers of patients, expressed as percentages of the total number (n=58), that fall into the following five categories: patients for whom *all* end-tidal isoflurane concentrations, observed in a 3-min period, were below ('too low'), within (≥0.8 vol% and ≤1.1 vol%), or above ('too high') the therapeutic window, and of those with isoflurane concentrations crossing the 0.8 or 1.1 vol% boundary in the same period of time. The data total 100%. For example, from 12–15 min the isoflurane concentrations were 'within the therapeutic window' for 60%, 'too low' for 26%, and 'crossing 0.8 vol%' for 14% of the patients.

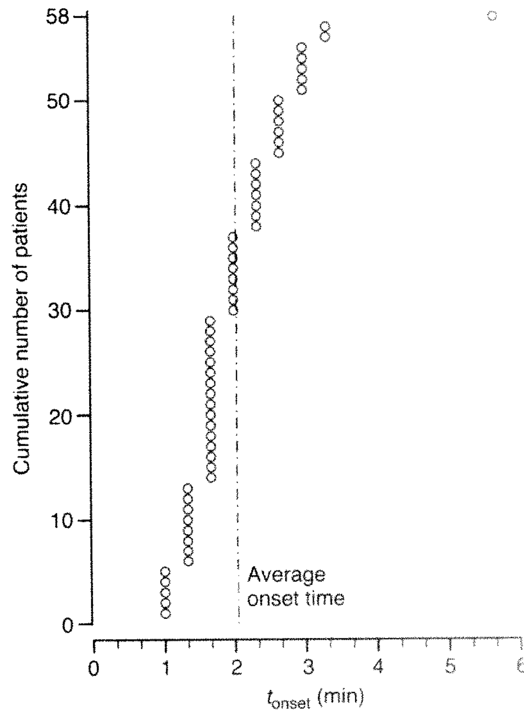

Fig 5 Detailed analysis of the first 7 min: distribution of individual onset times (t_{onset}) for end-tidal isoflurane concentrations, that is the time needed to attain the therapeutic window. Each patient is represented by one symbol (open circle): 95% of the population (55 out of 58 patients) had an onset time ≤3 min. The aim was that end-expired isoflurane concentrations would enter the desired window in less than 5 min.

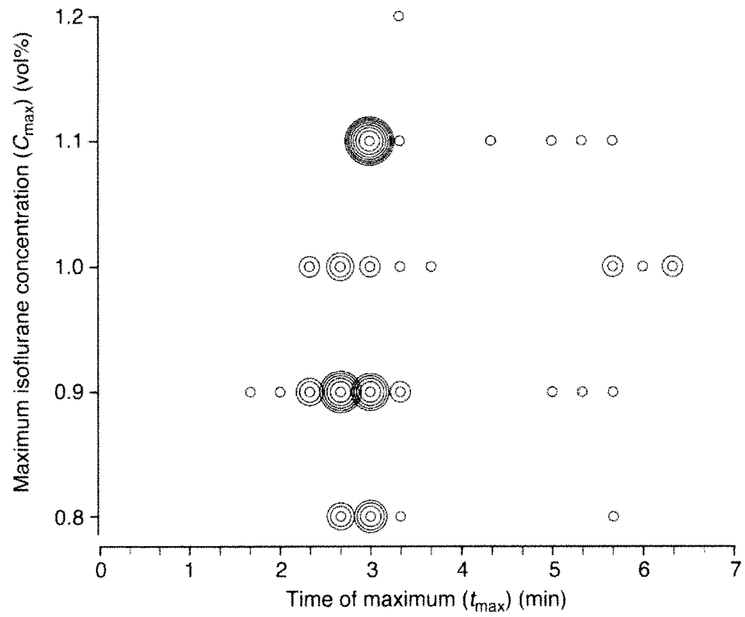

Fig 6 Detailed analysis of the first 7 min: scatter plot of maximum end-expired isoflurane concentration (C_{max}) by time of maximum (t_{max}). Each patient is represented by one open circle (n=58). Circles to be plotted on the same point remain visible by adjusting their radii to the number of observations at the same point.

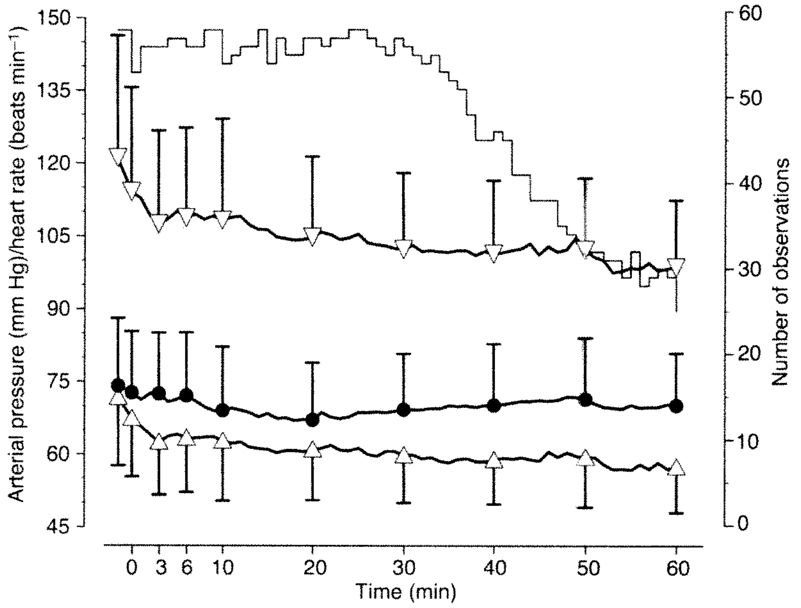

Fig 7 Haemodynamic variables. The SAP and DAP and the heart rate are shown (left y-axis) along with the number of observations (step plot without symbols; right y-axis). The heavy lines represent means of arterial pressures and heart rate. The spread of data is reflected by 1 SD in the positive (SAP and heart rate) or negative direction (DAP) at −1, 0, 3, 6, and 10 min, and at 10-min intervals thereafter. Time zero is the start of isoflurane administration.

reading of less than 0.8 vol% really means less than 0.75 vol%. With an SD of approximately 0.1 vol%, this means that only those patients more than 0.5 SD below the mean concentration will be classed as 'too low' which, for a Gaussian distribution, would be 31%, in better agreement with Table 4.

An upward trend in end-expired concentration in the 15–60 min period was found experimentally as well as in the model (Fig. 3). The slope was only 80% that in the model but still suggests that uptake was not constant in that period. This agrees with recent findings,[6] but conflicts with the interpretation of other work.[7]

Although scheme C is less economical than B, there is a practical argument (other than rapid induction with isoflurane) to use more than 1 litre min^{-1} during the early stages of anaesthesia. Nitrous oxide uptake may still be unpredictably high. Using a total FGF of 3 and 1.5 litre min^{-1}, each for 3 min, helps to prevent lack of gas in the circle system. If a shortage of fresh gas should occur, ventilation may be less than optimal, alarms may need to be silenced, and time-consuming adjustments of the Rotameters would be necessary.

There are clinically important arguments against the use of schemes A and B, both using 5 and 4 vol% isoflurane. At such high settings, vaporizer output may deviate more from that set on the dial than at lower settings.[8 9] Thus, schemes A and B may prove to be less reliable than C. Furthermore, scheme C requires less adjustments than A or B and these occur in a shorter time period (Table 1). Nevertheless, scheme A might be a good choice for those who wish to use a FGF $\geqslant$1 litre min^{-1}. Obviously, scheme A lacks clinical testing.

We have found that scheme C is appealing and easily remembered. Although it reflects 'very-nearly-closed-circuit anaesthesia',[10] it does not have a steep learning curve, and trainees remember the scheme well after using it for only a few anaesthetics. The combination of three times the number three appears to be a key factor. Indeed, the (three-step) scheme starts with 3 vol% isoflurane in a 'full flow' of 3 litre min^{-1} for 3 min. This is followed by a 'half flow' of 1.5 litre min^{-1}, again for 3 min, and 'minimal flow' of 0.5 litre min^{-1} thereafter.

Clear caveats have to be made about clinical implementations of theoretical results.[5] Scheme C was never intended to be used as a rigid recipe, but rather as a 'rule of thumb' or starting regimen that should be adjusted to the individual needs of the patient.[11] Valuable tools for that purpose are sound clinical judgement and appropriate monitoring of concentrations of anaesthetic as well as haemodynamic variables. Rapid build-up of concentrations of a potent inhalation anaesthetic can have clinically important haemodynamic consequences. Thus, a short interval time for the assessment of NIBP is necessary during the early phases, especially in the absence of surgical stimulation.

Similarly, measurement of the inspired oxygen tension is indispensable when using fixed low flows with nitrous oxide. Under 'minimal-flow' conditions, nitrous oxide accumulates in the circuit because nitrous oxide uptake diminishes as time passes.[4] It follows that, oxygen uptake being unchanged, the oxygen tension decreases with time (Fig. 6 in ref. 2). In accordance with the findings[4] of Virtue, 200 ml min^{-1} of nitrous oxide in 300 ml min^{-1} of oxygen appears to be the right base for an idealized 70 kg patient (Fig. 2). Nevertheless, inspired oxygen fractions less than 0.3 may develop, especially in patients weighing more than average. This occurred in five patients with a median body mass of 92 kg (range 76–126 kg) for $\geqslant$5 min in the first 120 min of the anaesthetic, while Sp_{O_2} was always $\geqslant$92%. Monitoring must permit early correction of FGF.

Anaesthetists often point out that the main disadvantage of low-flow techniques is that the inspired anaesthetic gas concentration is not directly related to the vaporizer setting. One must realize, however, that the inspired concentration is a clinically less important value than the end-expired concentration, because the effects of inhaled anaesthetics are related to the latter.

Our results suggest that a three-step scheme using 3 vol% isoflurane in a 'full flow' of 3 litre min^{-1} and a 'half flow' of 1.5 litre min^{-1}, each for 3 min, with 'maintenance' of 0.5 litre min^{-1} thereafter, is an easily remembered dosing strategy maintaining an end-expired concentration of approximately 1 vol% for 60 min. As a rapid induction with a potent volatile anaesthetic agent is obtained, close monitoring of vapour concentrations and haemodynamic variables is mandatory.

Acknowledgement

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Bispectral index monitoring during electroconvulsive therapy under propofol anaesthesia

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Background. The accuracy of the bispectral index (BIS) as a monitor of consciousness has not been well studied in patients who have abnormal electroencephalograms (EEG).

Methods. We studied the changes in BIS, its subparameters, and spectral entropy of the EEG during 18 electroconvulsive treatments under propofol and succinylcholine anaesthesia. A single bifrontal EEG, and second subocular channel (for eye movement estimation) was recorded.

Results. The median (interquartile range) BIS value at re-awakening was only 57 (47–78)—thus more than a quarter of the patients woke at BIS values of less than 50. The changes in spectral entropy values were similar: 0.84 (0.68–0.99) at the start, 0.65 (0.42–0.88) at the point of loss-of-consciousness, 0.63 (0.47–0.79) during the seizures, and 0.58 (0.31–0.85) at awakening.

Conclusions. Post-ictal slow-wave activity in the EEG (acting via the SynchFastSlow subparameter) may cause low BIS values that do not correspond to the patient's clinical level of consciousness. This may be important in the interpretation of the BIS in other groups of patients who have increased delta-band power in their EEG.

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Keywords: monitoring, bispectral index; anaesthesia, depth; brain, electroconvulsive therapy; monitoring, electroencephalography; brain, entropy

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The bispectral index (BIS) is a processed electroencephalogram (EEG) parameter that purports to measure the level of hypnosis in anaesthetized patients. The BIS was formulated retrospectively using a large database of EEG recordings and clinical correlative data.[1] A literature search did not reveal any studies specifically evaluating the accuracy of the BIS in predicting the hypnotic level in patients with underlying abnormal EEG patterns. Tanabe and colleagues observed in a single patient that electroconvulsive therapy (ECT) may decrease BIS during continuous propofol infusion.[2] It has been observed that patients in the post-ictal state often display slow, delta, EEG waves even after they have regained consciousness.[3] We performed an observational study on a group of patients undergoing ECT to evaluate the effect of seizure and post-ictal activity on the BIS and its ability to track the level of hypnosis.

Methods

After obtaining regional ethics committee approval and written patient consent, the BIS was recorded during 20 ECT treatments in 13 patients (aged 28–72 yr). Patients having compulsory treatment under the mental health act were excluded. Apart from the primary psychiatric illness requiring ECT, one patient had a previous history of childhood epilepsy but was currently symptom-free and not on anticonvulsants. No other patients had any neurological illness. EEG electrodes (Zipprep, Aspect Medical Systems, Newton, MA, USA) were attached before induction and impedance checked to be below 10 KΩ. One bipolar EEG channel was recorded from the forehead (F7–F8, on the International 10–20 system). Because eye movements may look very similar to slow delta waves in the frontal EEG, a second channel was recorded from the cheek with electrodes placed diagonally below the right eye to detect eye movement artifact.[1 4] The eye movements (EYE) were quantified using the standard deviation (SD) of the amplitude from channel two.

Recording was commenced using an Aspect A-1000 EEG monitor (software version 3.31, Aspect Medical Systems), and data downloaded to a portable computer for storage and analysis. The sampling rate was 128/s, and the filters set at

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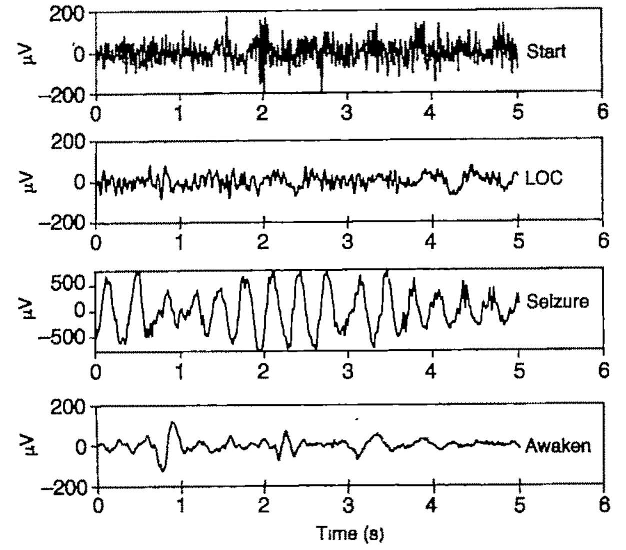

Fig 1 Typical examples of the changes in the raw EEG waveform at various stages of the anaesthetic

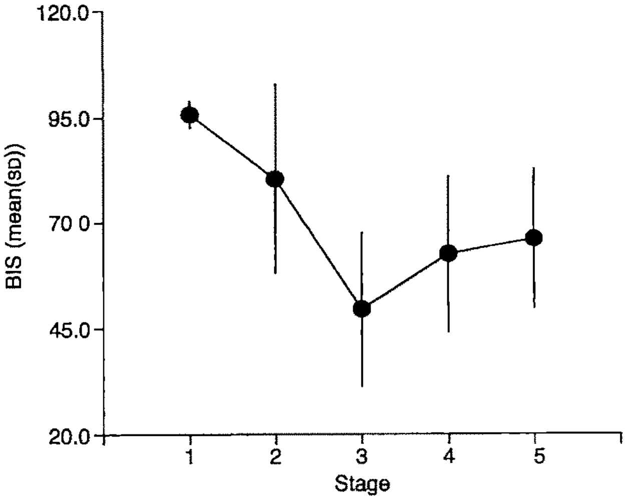

Fig 2 Changes in the BIS at various stages during the anaesthetic The bars indicate the SD. Stage 1=T1, 2=T2, 3=T3, 4=T4, 5=T5.

0.5 and 70 Hz. An anaesthetist uninvolved with the study gave their 'usual' anaesthetic consisting of: induction with propofol (70–170 mg i.v.) and neuromuscular block with succinylcholine (45–60 mg i.v.). Times were recorded for the following events: (1) start of induction (T1); (2) loss of response to verbal command (T2); (3) 10 s after the end of the electroconvulsive shock (T3); (4) first eye opening to verbal command (T4); and (5) 1 min after first eye opening (T5).

The data were analysed using Matlab (Matlab 5.3, The Mathworks Inc., Natick, MA, USA). The subparameters of the BIS (the BetaRatio and the SynchFastSlow) were calculated using published algorithms.[1] Burst suppression was not observed during convulsions or in the post-ictal phase. Because there is some evidence that the spectral entropy of the EEG signal is a promising measure of depth of anaesthesia, this parameter was also calculated as described by Inoue.[5] We used the frequency-band 2–40 Hz, and a resolution of 1 Hz.

Results

Two recordings had to be excluded because of technical faults in recording. Typical examples of the raw EEG at the various times are shown in Figure 1. The changes in the BIS values at each of the five time-points are shown in Figure 2. It can be seen that the BIS during the seizure has very low values (median=45 (25–75th percentiles 39–59)), and that at the point of awakening the median value is only 57 (47–78), rising to 67 (54–83) 60 s later. Thus, over a quarter of the patients woke at BIS values of under 50. Almost all of these patients continued to have low BIS values 1 min later, indicating that this phenomenon could not be explained as 'computational lag' by the Aspect monitor.[1] These BIS values are significantly lower ($P<0.01$) than those we obtained in a separate, previously published study, which involved similar dosages of propofol in patients having cardioversion.[6] In this previous study the patients awoke at median (25–75th percentiles) BIS values of 79 (73–84), which increased 60 s later to 90 (85–95).

Figure 3 shows the changes in the two calculated subparameters of the BIS at each stage. It can be seen that the BetaRatio returns to near-pre-induction levels at the point of awakening, whereas the SynchFastSlow remains low—suggesting that the SynchFastSlow subparameter is predominant in depressing the BIS during the patient's recovery phase. We conducted a backward-selection step-wise multiple linear regression of possible explanatory factors that may be correlated with the BIS at the point of awakening. The possible explanatory variables included in the initial regression model were: BetaRatio, SynchFastSlow, EYE, total spectral power, relative spectral power in the gamma (40–47 Hz), alpha (10–20 Hz), and delta (1–5 Hz) wavebands, and frontalis EMG activity – logarithmic power in 55–64 Hz band. Only SynchFastSlow and EYE remained in the final model as significant independent predictors of the BIS at the point of awakening (overall model $R^2=0.39$, $P=0.001$). The model was:

$$\mathrm{BIS}_{(\mathrm{T4})}=118.1\ (\mathrm{SE}=14.3,\ P<0.0001) + 13.4\ (\mathrm{SE}=5.3,\ P=0.016) \times \mathrm{SynchFastSlow} -8.6\ (\mathrm{SE}=2.2,\ P=0.007) \times \mathrm{EYE}.$$

The median (25–75th percentiles) values of the spectral entropy at the start were 0.84 (0.68–0.99), dropping to 0.65 (0.42–0.88) at the point of loss-of-consciousness, and further decreasing to 0.63 (0.47–0.79) during the seizures. Spectral entropy did not increase at the point of awakening (0.58 (0.31–0.85)). The value at awakening was significantly different from the start value ($P=0.001$, paired *t*-test), but not different from the value during the seizures ($P=0.44$,

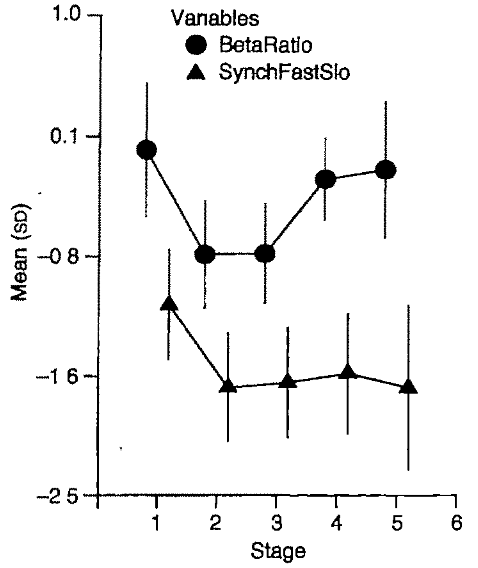

Fig 3 Changes in the subparameters of the BIS at various stages during the anaesthetic The bars indicate the SD. Stage 1=T1, 2=T2, 3=T3, 4=T4, 5=T5. The subparameter values at time-points T4 and T5 are significantly lower than those at T1 for the SynchFastSlow (P<0.001, Wilcoxon Signed-Rank test), but not for the BetaRatio.

paired *t*-test). If the spectral entropy was calculated using only the higher frequencies of the EEG signal (20–40 Hz), the values at awakening (0.96 (0.86–0.99)) were significantly higher (P<0.001, *t*-test) than those calculated using the whole range of frequencies (2–40 Hz).

Discussion

We have found that following ECT, over one-quarter of the patients re-awaken at a BIS value that is considered to reliably indicate unconsciousness (<50), when applied to the normal surgical population. This finding has two consequences. First, monitoring the BIS following ECT may not reliably correlate with the patient's clinical level of consciousness. More importantly it suggests that, in other disease states in which there is increased delta EEG activity in conscious patients, the BIS may be falsely low. The question of whether this generalization is true warrants further investigation. Increased slower EEG activity (delta and theta) is common in both schizophrenic patients, and the elderly.[7–10]

Which subcomponent of the BIS was responsible for the falsely depressed values? The BetaRatio recovered towards pre-induction levels at the time of first eye-opening to verbal command and at 60 s after, but the SynchFastSlow remained low. This may be explained by the presence of low-frequency (delta) EEG activity in the post-ictal state. Because of the denominator used in the respective calculations, activity below 10 Hz will affect the calculation of the SynchFastSlow, but not the BetaRatio.[1] The regression model was derived from only 18 data points, and therefore must be interpreted with caution, but supports the predominance of the SynchFastSlow in lowering the BIS during recovery.

The spectral entropy calculated at each stage showed changes that were similar to those shown by the BIS. Neither parameter increased reliably at the point of awakening. However, the behaviour of the spectral entropy is somewhat dependent on technicalities of the range of frequencies over which it is calculated, and the amount of pre-processing and filtering. If the spectral entropy was calculated over higher frequencies (e.g. 20–40 Hz) it is sensitive to increases in higher frequency activity that are characteristic of the return of consciousness.[11] However it is difficult to be sure how much of this activity is frontal EMG, and how much is true return of high-frequency EEG 'gamma' rhythms at the point of awakening. Conversely, if the lower frequencies are excluded, then the spectral entropy will be less sensitive to the influence of the strong delta rhythms that indicate deep anaesthesia. One may speculate that in order to cover fully the range of anaesthetic concentrations and effects it would be logical to have a 'meta-function' that varied and combined the influence of different frequency-bands in the spectral entropy calculations. This is analogous to the construction of the BIS. If the value of the spectral entropy (20–40 Hz) was high (e.g. >0.9) it would predominate. As the high-frequency spectral entropy (20–40 Hz) fell, then the proportional influence of spectral entropies calculated using progressively lower frequencies (e.g. 2–20 Hz) would increase.

The interpretation of the EYE parameter is problematic. The diagonal placement of the eye electrodes should have been able to detect both horizontal and vertical eye movements. The EYE parameter decreased only minimally during the pre-ECT period when the patients were anaesthetized with propofol and paralysed with suxamethonium—as evidenced by minimal movements during the grand mal seizure. Because EYE still had activity when the patient was supposedly paralysed, this clearly indicates that the EYE parameter was not a pure estimate of eye-movements, but included an unknown and significant quantity of EEG signal and, possibly, frontalis EMG activity. Indeed, the BIS derived from the second (eye) channel correlated well with the true channel-one BIS (derived from the frontal montage) when the patient was anaesthetized—Pearson's correlation coefficient (r): $r_{(T2)}$=0.99, $r_{(T3)}$=0.97, $r_{(T4)}$=0.95, $r_{(T5)}$=0.57.

In conclusion, our study suggests that a low BIS value does not correspond to a deep hypnotic level in patients after ECT. By inference, this may also be applicable to patients with other pre-existing EEG abnormalities. In our patient group, the recovery of spectral power in the higher frequencies (as estimated by the BetaRatio, or spectral entropy (20–40 Hz)) was more predictive than the BIS, and the broadband spectral entropy (2–40 Hz), of the recovery of consciousness.

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Effect of hypothermia on brain tissue oxygenation in patients with severe head injury

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Background. There is renewed interest in the use of induced hypothermia as a method of neuroprotection both intraoperatively and in the intensive care management of severe brain injury. In this study we have investigated the effects of hypothermia on brain tissue oxygenation in patients with severe head injury.

Methods. Thirty patients with severe head injury (Glasgow coma score <8) were monitored with a multimodal sensor inserted into the brain which measures tissue P_{O_2}, P_{CO_2}, pH and temperature in addition to routine monitoring. Patients were cooled to a minimum of 33°C when clinically indicated.

Results. For all 30 patients brain and systemic temperature correlated well (r=0.96). Brain temperature was consistently higher than systemic temperature by 0.41±0.26°C (confidence limits). Brain tissue P_{O_2} decreased with hypothermia, with a significant reduction below 35°C (P<0.05).

Conclusions. These results emphasize the advantage of measuring brain temperature directly, and suggest that decreasing brain temperature below 35°C may impair brain tissue oxygenation.

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Keywords: brain, injury; brain, tissue oxygenation; complications, hypothermia

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Important advances have been made in understanding the mechanisms of secondary brain damage in patients with severe head injury. Attempts to interfere pharmacologically with these mechanisms have so far been unsuccessful.[1]

Hypothermia has been used as a method of brain protection in a clinical setting in patients with traumatic brain injury for many years. Moderate hypothermia (temperature 32–34°C) in animal models of focal and global ischaemia and traumatic brain injury has been shown to reduce secondary brain injury and improve behavioural outcome.[2–5] There are also clinical reports of patients with traumatic brain injury treated with moderate hypothermia (32–33°C for 24 h) suggesting hastened neurological recovery and an improved outcome in a subgroup of patients.[6] In addition to cerebral metabolic suppression, hypothermia has also been found to modify a number of molecular responses such as the release of excitatory amino acids,[7] cytokines,[6 8] free radicals[9] and inflammatory mediators.[10] However, in an animal model of transient global ischaemia, Bacher *et al.* demonstrated that brain tissue oxygen was no better preserved during hypothermic ischaemia compared with normothermic ischaemia.[11] In this study we have investigated the effects of decreasing brain temperature on indices of brain parenchymal oxygenation and metabolism in patients with severe head injury.

Methods

Patients

As part of a prospective study of continuous multimodal monitoring in head-injured patients, data from 30 patients with severe head injury (Glasgow coma score [GCS] <8) who were admitted to our neuro intensive care unit were analysed. All patients were managed according to the protocol for severe head injury followed on our neuro intensive care unit.[12] This included sedation with propofol (3–5 mg kg^{-1}h^{-1}), fentanyl (1–2 µg kg^{-1} h^{-1}) and paralysis with atracurium 0.5 mg kg^{-1} h^{-1}. Before induction of hypothermia, propofol was changed to midazolam (0.1–0.2 mg kg^{-1} h^{-1}). Mean arterial pressure was also manipulated to achieve a cerebral perfusion pressure (CPP) greater than 70 mm Hg, with the use of fluid loading and

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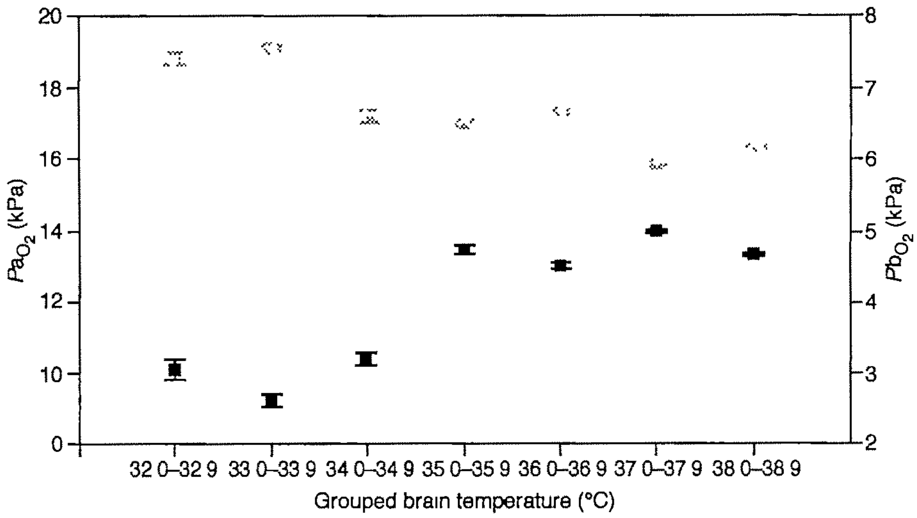

Fig 1 Changes in arterial and brain tissue oxygen (Pa_{O_2}, grey squares and Pb_{O_2}, black squares, respectively) with temperature Values are given as mean (±95% confidence limits) for grouped brain temperature values Data were analysed within criteria of cerebral perfusion pressure >50 mm Hg and arterial CO_2 4–5 kPa

dopamine (up to 15 μg kg^{-1} min^{-1}). If required, norepinephrine was also started at a rate of 0.5 μg kg^{-1} min^{-1}.

Monitoring

All patients had routine invasive monitoring applied, which included mean arterial pressure, central venous pressure, intracranial pressure (ICP) (Codman, Raynham, USA) and continuous jugular bulb oximetry (Sj_{O_2}; Baxter, Northampton, UK). Pulmonary artery catheters were inserted into those patients requiring inotropic support, those with pre-existing cardiac disease and those with significant myocardial contusion. In addition, and after Institutional Ethics Committee approval and written consent from the next of kin, multimodal sensors were inserted to measure brain and arterial O_2, CO_2, pH and temperature. After calibration with three precision gases, two sensors (Paratrend 7, Diametrics Medical, High Wycombe, UK) were inserted into each patient. One was inserted through an 18-gauge cannula into a femoral artery for continuous blood-gas analysis. The second was inserted into brain tissue through a specially designed bolt[13] which was placed in the non-dominant frontal region of the skull.

Hypothermia was induced when ICP was sustained above 25 mm Hg after standard medical treatment. The patient's core temperature was reduced to a target temperature of 33°C using an air cooling system (Bair Hugger™, Augustine Medical, Eden Prairie, MN, USA) and cold fluids. Brain and arterial blood temperatures were measured by the respective Paratrend sensors. Haemodynamic variables, ICP, temperature and Paratrend data were downloaded onto a computer and time averaged over 2 min. Hypothermia therapy was continued until control of ICP <25 mm Hg was achieved.

Statistical analysis

Data were analysed using a Tukey-HSD one-way analysis of variance (SPSS package) with a significance level of 0.05. Multivariate linear regression was used to calculate the correlation coefficient between arterial and brain temperature. Analysis of oxygen and Sj_{O_2} was performed for data with the criteria of CPP >50 mm Hg, and arterial CO_2 4–5 kPa. Analysis of CO_2 and pH was performed for data within the criteria of CPP >50 mm Hg. Data are expressed as mean (±95% confidence limits).

Results

Patients

Thirty patients (22 male, 8 female), all with GCS <8, were monitored for up to 14 days (mean 5 days). The mean age was 39 yr (range 17–78). Seventeen patients had their brain temperature reduced below 35°C. Data from all 30 patients were pooled for analysis.

Temperature measurement

Analysis of all 30 patients revealed a close correlation between arterial and brain temperature (r=0.96, P<0.001). In individual patients, brain temperature was found to be higher than arterial temperature. The mean (SD) difference between the sites was 0.41 (0.26)°C.

Brain and arterial Po_2, Pco_2 and pH

Figure 1 shows the changes in mean brain tissue oxygen (Pb_{O_2}) and arterial oxygen concentration (Pa_{O_2}) with brain temperature reduction. There is a significant decrease in

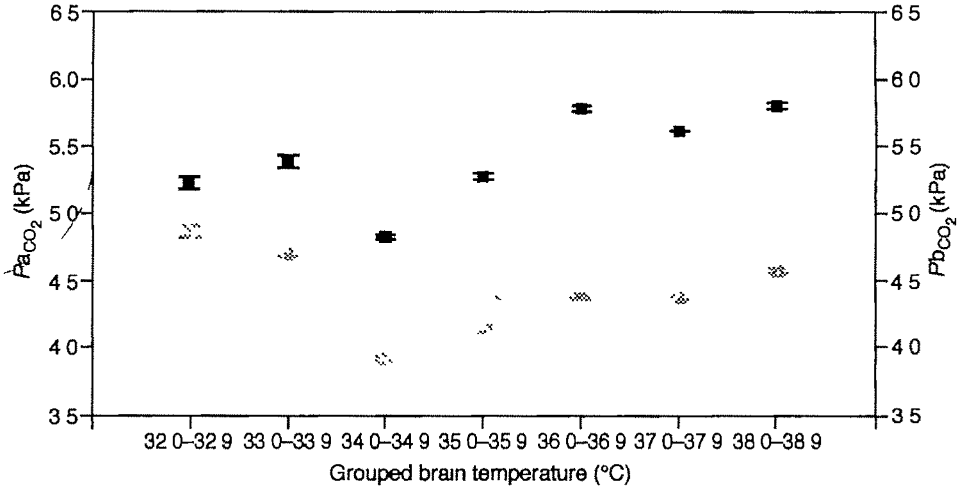

Fig 2 Changes in arterial and brain tissue carbon dioxide concentration (Pa_{CO_2}, grey squares and Pb_{CO_2}, black squares, respectively) with brain temperature. Values are given as mean (±95% confidence limits). Data were analysed within the criterion of cerebral perfusion pressure >50 mm Hg

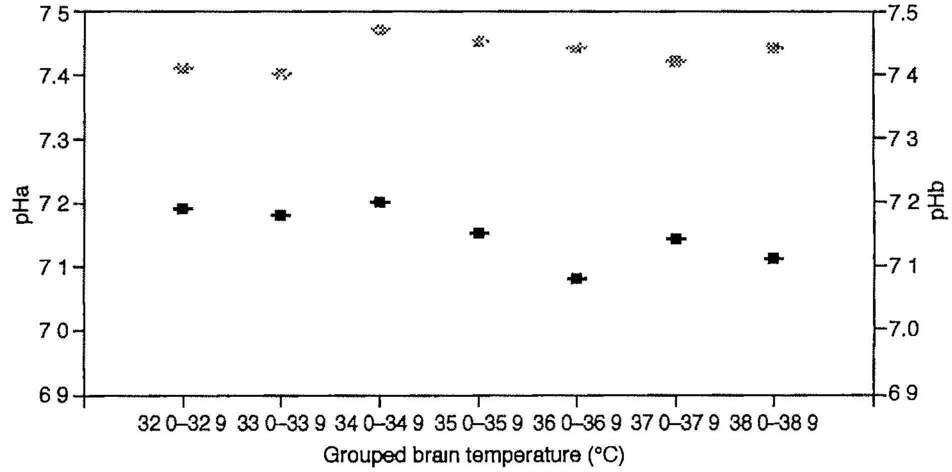

Fig 3 Changes in arterial and brain tissue pH (pHa, grey squares and pHb, black squares, respectively) with brain temperature. Values are given as mean (±95% confidence limits) Data were analysed within the criterion of cerebral perfusion pressure >50 mm Hg.

Pb_{O_2} below 35°C ($P<0.05$) with a highly significant reduction below 34°C ($P<0.001$) compared with 37°C, whereas Pa_{O_2} increased below 37°C. Brain tissue and arterial CO_2 (Pb_{CO_2}, Pa_{CO_2} respectively) both decreased with reduced brain temperature to a temperature of 34°C, below which CO_2 increased (Figure 2). Very little change occurred in brain tissue or arterial pH with temperature, as shown in Figure 3. Sj_{O_2} increased with reduction in temperature (Figure 4).

Discussion

Brain temperature is generally estimated using indirect methods from easily accessible sites such as the rectum, oesophagus or tympanic membrane. In order to avoid the detrimental effects of hyperthermia[14] and maximize the potential beneficial effects of induced hypothermia, it is essential to know the temperature gradients between these sites and the brain. The results of this study show that brain temperature is greater than arterial temperature, with a mean difference of 0.41°C. Gradients of between 0.5 and 2°C have been demonstrated in other studies.[6 15 16] The importance of direct brain temperature measurement is emphasized by the variability between systemic and brain temperature and the inability to identify the most appropriate site for measuring core temperature.[17]

The data show that as brain temperature is reduced to 35°C, there is no significant change in brain tissue O_2, CO_2 and pH. The increase in Sj_{O_2} observed below 37°C is most likely the result of cerebral metabolic suppression resulting in a reduction in oxygen extraction from cerebral tissue. Below 35°C, however, there is a significant reduction in Pb_{O_2} which occurs despite an increase in Pa_{O_2}. Arterial P_{CO_2} and Sj_{O_2} also increase, although there is little change in

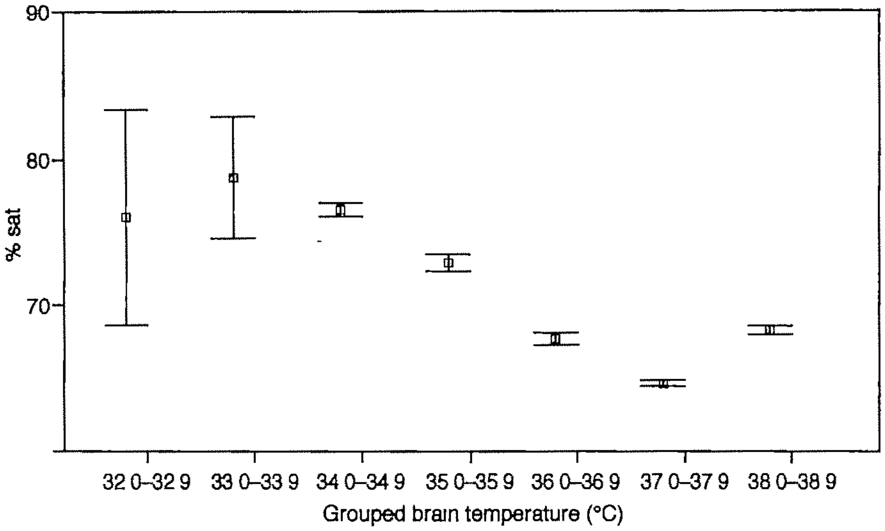

Fig 4 Changes in jugular venous oxygen saturation (Sj_{O_2}) with brain temperature. Values are given as mean (±95% confidence limits) Data were analysed within the criteria of cerebral perfusion pressure >50 mm Hg and arterial CO_2 4–5 kPa.

tissue or arterial pH. Although the target temperature for induced hypothermia was 33°C, there was some overshoot in a number of patients, with brain tissue temperatures decreasing below 33°C but not below 32°C. Data were collected in these patients but were not significantly different from those at 33°C for all measured variables.

The increase in Sj_{O_2} with decreasing brain temperature is a predictable response to the global reduction in brain metabolism. However, the reduction in Pb_{O_2} (in association with maintenance of Pa_{O_2}) below 35°C suggests that although reduction in brain metabolism is undoubtedly a factor contributing to these changes, other mechanisms may be involved. While well oxygenated blood is arriving at the capillaries, oxygen is not being transferred efficiently to the extracellular compartment. One factor contributing to this may be the leftward shift of the oxygen dissociation curve associated with hypothermia. This enhances the affinity of oxygen to haemoglobin, causing reduced oxygen release and thereby reducing the availability of oxygen to diffuse into cells.

An oxygen delivery/metabolism mismatch may develop after head injury,[18] and may result from a combination of diffusion abnormalities (microvascular failure), arteriovenous shunts directing flow away from capillaries, increased diffusion distances because of cytotoxic oedema, or mitochondrial abnormalities resulting from membrane alterations. These factors combined with the reduced availability of oxygen at the capillary level as described above would contribute to impaired diffusion of oxygen into the mitochondria and relative tissue hypoxia.

Differences in methods of measurement may also be a factor in these observations. Jugular bulb oximetry is an established method of measuring global cerebral oxygenation. The major limitation of this technique is that regional changes in cerebral oxygenation may not be detected unless the changes are large enough to affect the global measurements. It is accepted that regional variations in brain temperature occur as a result of the heterogeneous nature of cerebral blood flow and metabolism. Changes in brain temperature will therefore affect both global and regional brain oxygenation. Thus, the regional variations of brain oxygenation arising from changes in brain temperature may not be detected by jugular venous oximetry. Tissue sensors, however, have been shown to be a more sensitive measure of regional oxygenation compared with Sj_{O_2},[19] and will therefore be more likely to detect these regional changes.

The small changes in tissue pH with hypothermia reflected changes in arterial pH, indicating that ischaemic acidosis was probably not occurring. There are two possible explanations. First, the development of tissue acidosis during cerebral ischaemia in human brain has been shown to be slower with deep hypothermia (18°C) compared with mild hypothermia.[20] Secondly, the Paratrend sensor measures pH and CO_2 by the pH-stat method, which corrects for the actual temperature of the patient. This produces relative hypercarbia because of the increased solubility of CO_2 during hypothermia. If the alternative α-stat method were used (pH and CO_2 measurement corrected to 37°C), changes in pH may have become more apparent. Evidence from *in vitro* preparations has suggested that the α-stat method applies during hypothermia and that there are similarities in the effect of hypercarbia and moderate hypothermia on postischaemic recovery in tissue pH, with additive detrimental effects.[21]

Our results demonstrate that brain parenchymal oxygenation is maintained with induced hypothermia to 35°C. Below this temperature Pb_{O_2} is not preserved, which supports the findings in an animal model of transient global ischaemia.[11] Although the effect of induced moderate hypothermia on outcome has not been addressed in this study, a recent multicentre trial has demonstrated no beneficial effect of hypothermia to 33°C in traumatic brain injury.[22] Our results imply that the neuroprotective effects of induced hypothermia may be most beneficial at a temperature of 35°C. Hypothermia below this level results in impairment of cerebral oxygenation. The precise mechanisms of these changes require further investigation.

Acknowledgements

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Cardiovascular effects of simultaneous occlusion of the inferior vena cava and aorta in patients treated with hypoxic abdominal perfusion for chemotherapy[†]

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Background. Animal studies suggest less cardiovascular disturbance if the aorta and vena cava are occluded simultaneously. We set out to establish the effects of simultaneous clamping in humans, because oncologists suggested that perfusion for chemotherapy could be done under local anaesthesia without invasive haemodynamic monitoring.

Methods. We studied the cardiovascular effects of the onset and removal of simultaneous occlusion of the thoracic aorta and inferior vena cava, in seven ASA II patients. Two stop-flow catheters positioned in the aorta and in the inferior vena cava were inflated to allow hypoxic abdominal perfusion to treat pancreatic cancer. We measured the arterial pressure, heart rate (HR), right atrial pressure (RAP), pulmonary artery pressure (PAP), pulmonary artery wedge pressure (PAWP) and cardiac output (CO), and calculated systemic vascular resistance index (SVRi), pulmonary vascular resistance index (PVRi), left ventricular stroke work index (LVSWi) and right ventricular stroke work index (RVSWi). Three patients were studied with transoesophageal echocardiography.

Results. Six patients needed intravenous nitroprusside during the occlusion because mean arterial pressure (MAP) increased to more than 20% of baseline (SVRi increased by 87%). One minute after occlusion release, all patients had a 50% decrease in MAP, and mPAP increased by 50%. The procedure had severe cardiovascular effects, shown by a 100% increase in cardiac index at occlusion release with increases in left and right ventricular stroke work indices of 75% and 147%. Left ventricular wall motion abnormalities were seen on transoesophageal echocardiography.

Conclusions. Serious haemodynamic changes occur during simultaneous occlusion of the thoracic aorta and inferior vena cava, which may need invasive haemodynamic monitoring.

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Keywords: arteries, aorta occlusion; veins, vena cava inferior occlusion; heart, cardiovascular changes

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Clamping the aorta has major cardiovascular effects.[1] In animal studies, clamping the inferior vena cava at the same time can prevent large haemodynamic changes.[2 3] A single clinical report suggests that haemodynamic changes are not prevented by additional inferior vena cava occlusion.[4]

A percutaneous aortic ‘stop-flow’ infusion technique has been used for regional cytotoxic therapy of the abdomen for a number of malignant conditions.[5] The method aims to reduce the systemic side-effects of the chemotherapeutic drugs, whilst simultaneously potentiating the cytotoxic action of the drugs by hypoxia.[5–7] In our hospital, a phase I–II chemotherapy trial based on this hypoxic abdominal perfusion procedure (HAP) is taking place. The procedure achieves a greater dose and thus a greater local concentration of melphalan and mitomycin C with a 20-min isolation and perfusion of the abdomen.

The temporary vascular isolation of the abdominal cavity for this procedure is achieved with tourniquets placed around both upper thighs to exclude the lower limbs from

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[†] Part of this work was orally presented at the Dutch Society of Anaesthesiology 1999, Veldhoven, The Netherlands

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the circulation, and by surgical insertion of stop-flow catheters, one into the aorta and a second into the inferior vena cava, to isolate the abdominal circulation.

We wished to measure the haemodynamic effects of this simultaneous clamping in humans, because oncologists suggested that the procedure could be done using local anaesthesia and without invasive haemodynamic monitoring.

Table 1 Characteristics of the patients (mean and range)

Sex (F/M)	4/3
Age (yr)	57 (49–65)
Weight (kg)	67 (54–97)
Height (m)	1.72 (1.62–1.90)
Body surface area (m^2)	1.78 (1.61–2.03)
Additional diagnoses	Non-insulin dependent diabetes mellitus (n=1) Insulin-dependent diabetes mellitus (n=1) Sick sinus syndrome with AAI pacemaker (n=1)

Material and methods

Seven consecutive patients, all ASA II, were enrolled in the HAP phase I–II trial for locally advanced pancreatic cancer after diagnostic work-up, written informed consent, and explanation of the anaesthetic procedure. The perfusion study, using melphalan and mitomycin C, was approved by the local medical ethical committee. We excluded patients with significant cardiovascular disease (NYHA classes II, III or IV). Other patient characteristics are given in Table 1.

Anaesthetic management

On the evening before the operation the patients were premedicated with lorazepam 1 mg orally. On the day of operation, ranitidine 150 mg was added to their routine medication.

In the operating room, basic anaesthetic monitoring was started (HP M1166A OmniCare Anaesthesia Component Monitoring System Release F, Hewlett® Packard GmbH, Böblingen, Germany), followed by i.v. induction of anaesthesia with sufentanil 0.30 µg kg^{-1}, thiopental 5 mg kg^{-1} and vecuronium 0.1 mg kg^{-1}. After tracheal intubation, the lungs were ventilated with a closed-circuit anaesthetic machine (Physio BV, Haarlem, The Netherlands), using IPPV with settings of $F\text{I}_{\text{O}_2}$ 0.35 (oxygen–air mixture), frequency 14 min^{-1}, tidal volume 8 ml kg^{-1}, PEEP 5 cm H_2O, and I:E ratio 1:1.2. Respiratory frequency was adjusted to maintain Pa_{CO_2} between 4.5 and 5 kPa. Anaesthesia was maintained with isoflurane 0.9% end tidal and sufentanil 0.20 µg kg^{-1} i.v. was given at the start of the surgical procedure. Fluid management was standardized for all patients. Ringer's lactate was given by i.v. infusion, 20 ml kg^{-1} in the first hour of the procedure to correct the preoperative fluid restriction and venodilation caused by general anaesthesia, followed by 6 ml kg^{-1} h^{-1} for the rest of the procedure. Fluid management was not adjusted for any change in cardiovascular measurements. Sodium nitroprusside (SNP) i.v. was given as necessary to control MAP during the perfusion phase to within 20% of the preoperative value.

Additional monitoring was started. Blood pressure was measured using a radial artery cannula (Arrow radial artery catheterization set 20 Ga; Arrow Deutschland GmbH, Erding, Germany). A pulmonary artery balloon flow catheter (Arrow Thermo-Pace® Hands off® Heparin-coated Thermodilution Catheter 7.5 Fr. 5 lumen 80 cm catheter length; Arrow Deutschland GmbH) was passed through an introducer sheath (Arrow Percutaneous sheath introducer set 8.5 Fr; Arrow Deutschland GmbH) placed in the right internal jugular vein. A cardiac output measurement system (Baxter CO-set® closed injectate delivery system; Baxter Deutschland GmbH) was connected to the right atrial pressure (RAP) port of the thermodilution catheter. We used iced fluid. We studied three patients with per-operative transoesophageal echocardiography (TOE) (Sonotron Vingmed CFM 800; Vingmedsound Als, Horten, Norway) with a 5 MHz multi-plane transoesophageal echo (MPTE).

Surgical procedure

Tourniquets were placed around the upper thighs to allow isolation of the legs from the circulation. Then a small incision in the right groin was made to insert two catheters (arterial stop-flow catheter F12–600 mm and venous stop-flow catheter F12–600 mm; PFM Produkte für die Medizin GmbH, Köln, Germany) into the femoral artery and vein. They were advanced to above the coeliac trunk in the aorta and the level of the diaphragm in the inferior vena cava, using radiological control (Fig. 1). Heparin 5000 IU was given i.v.

The abdomen was then isolated. First, the tourniquets on both upper thighs were inflated to a pressure of 350 mm Hg. Then the balloon of the aortic catheter was inflated with a mixture of 25 ml NaCl 0.9% with contrast fluid and immediately afterwards the balloon of the caval catheter was also inflated. The maximum diameter of the balloons was 30 mm.

The cytotoxic drugs were perfused according to a set regimen using an extra-corporeal circuit connected to both catheters (Hypoxic perfusion set; PFM Produkte für die Medizin GmbH), flow rate, 250 ml min^{-1}. No oxygen was added to this extra-corporeal circuit. The perfusion of the chemotherapy was maintained for 10 min, followed by a 10-min period without drugs. After a total of 20 min hypoxic abdominal perfusion, the circulation to the abdomen was restored by deflation of the balloon in the aorta, followed immediately by deflation of the inferior caval vein balloon. After a stabilization period of 10 min the tourniquets were released from the thighs.

Data collection

ECG, MAP, heart rate (HR), RAP, mean pulmonary artery pressure (mPAP), blood temperature (measured by the

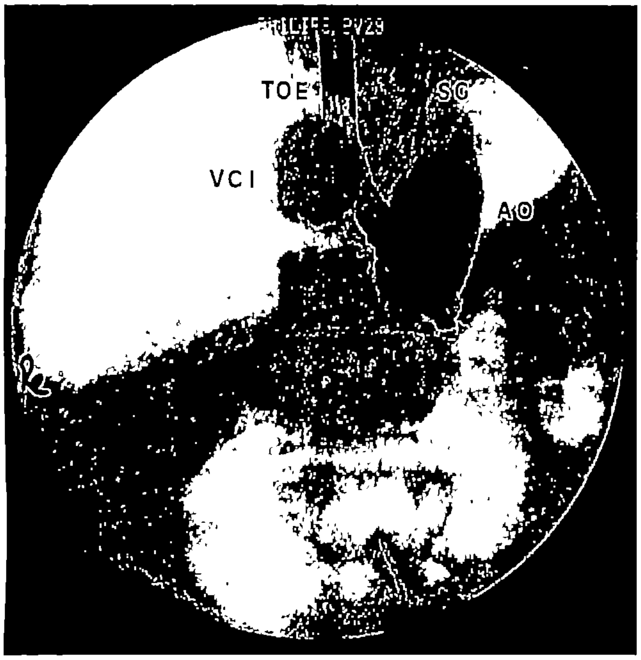

Fig 1 Radiograph taken during HAP phase, AO=aortic catheter, VCI= inferior caval vein catheter; TOE=transoesophageal echo probe, SG=Swan–Ganz catheter (see text for details).

thermodilution catheter) and peripheral oxygen saturation ($S\text{p}_{O_2}$) were measured continuously, and a record made of the values for each minute of the procedure.

Measurements were noted at previously defined times; these were 'steady state' (SS), during stable anaesthesia before tourniquet inflation; 'legs separated' (LS), when the tourniquets around the thighs were inflated; early in the 'HAP phase' (HAPa), just after complete abdominal isolation; late in the 'HAP phase' (HAPb), within 5 min before removal of occlusion; 'abdominal recirculation' (AR), when only the balloons of the catheters were deflated; 'complete recirculation' (CR), the tourniquets were also deflated; and 'end operation' (EO), just before reversal of anaesthesia was started. Cardiac output (CO) (measured in triplicate) and pulmonary artery wedge pressure (PAWP), measured just before CO, were measured at these times. If i.v. SNP was given during the perfusion phase, the infusion of SNP was turned off after determination of HAPb, but at least 4 min before abdominal reperfusion started. The time needed for the surgical preparation varied so that the time between SS and LS was a mean 47 min (range 30–65 min); thereafter, a rigid time schedule was maintained starting with the separation of the legs. Thus, LS was defined as t=0 min; HAP, t=4 min; AR, t=24 min; CR, t=34 min; EO, t=54 min. Cardiac index (CI), stroke index (SI), systemic vascular resistance index (SVRi), pulmonary vascular resistance index (PVRi), left ventricular stroke work index (LVSWi) and right ventricular stroke work index (RVSWi) were calculated with standard formulae. For each patient, these calculations were done using continuously measured variables that had been collected at the same time-points that CO was measured. Because CO and PAWP were measured 'early in the HAP phase' and not for instance always at 'the third minute of the HAP-phase', it was not possible to construct an exactly time-related set of the values of these intermittently measured variables for the entire group. The function of the left ventricle was monitored by TOE, with a transgastric short axis mid-papillary view, continually recorded on VHS videotape. Left ventricle end diastolic area (LVEDA) and left ventricle end systolic area (LVESA) were traced by the contouring program of the TOE device Fractional area change was calculated [(LVEDA − LVESA) / LVEDA×100] and left ventricular wall motion was classified with a semi-quantitative scoring system:[8] a normally contracting wall segment is scored as 1, mild hypokinesis as 2, severe hypokinesis as 3, akinesis as 4, and dyskinesis as 5. The left ventricular wall motion score index (LVWMSi) was calculated from the sum of all scores, divided by the number of segments observed.

Statistical analysis

Results are expressed as mean and standard deviation (SD) unless otherwise indicated. Statistical analysis was with SPSS for Windows, version 10.0. Data were analysed with a Wilcoxon signed ranks test to compare the observed mean difference between a value of a defined time point with the value at SS as recommended by Myles and Gin.[9] A P-value <0.05 was considered significant.

Results

Figures 2 and 3 show the time course of changes in the continuously measured values MAP, HR, RAP, mPAP and temperature.

With simultaneous clamping, MAP quickly increased to greater than 120% of the preoperative value in six patients. To control MAP within 20% of this value, i.v. infusion of SNP was started. This infusion was continued until the end of the HAP phase to control MAP. Although the SNP infusion was stopped at least 4 min before balloon deflation, a 50% reduction in MAP occurred in all patients in the first minute after balloon deflation. One minute later, however, MAP recovered spontaneously (Fig. 2).

The pacemaker of the patient with the sick sinus syndrome was set at a fixed rate of 70 beats min^{-1} Except for HR, the haemodynamic changes in this patient were comparable with the changes measured in the other six patients. HR increased by 42% during the second part of the HAP phase (Fig. 2).

RAP changed little despite the other cardiovascular changes, except at the fourth and fifth minute after the abdominal clamping, when it increased by 15% (Fig. 3).

Three minutes after balloon deflation, all the patients developed pulmonary hypertension; mPAP increased by 50% (Fig. 3).

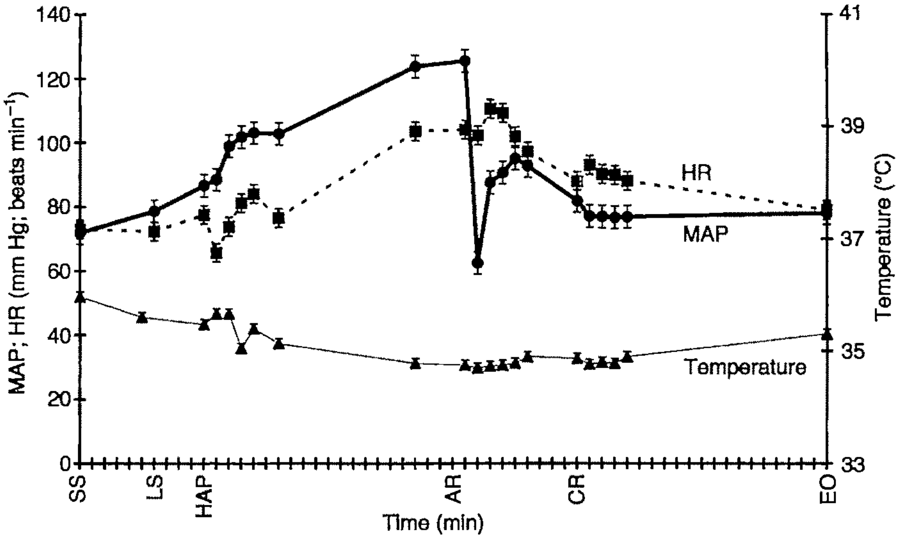

Fig 2 HR, MAP and temperature during the HAP procedure. Each bar on the abscissa represents one minute Data are mean (SE).

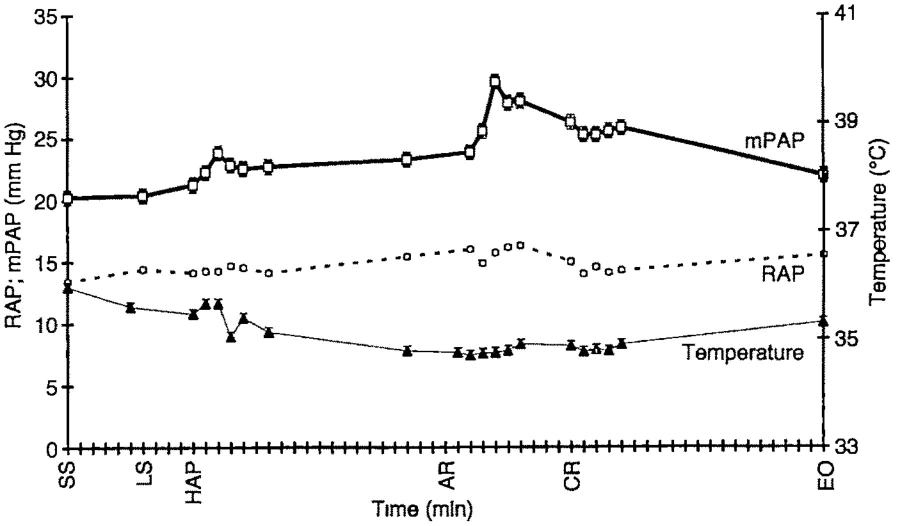

Fig 3 RAP, mPAP and temperature during the HAP procedure. Each bar on the abscissa represents 1 min. Data are mean (SE).

Table 2 shows the time course of changes in PAWP, CI, SI, SVRi, PVRi, LVSWi and RVSWi.

TOE was done in three patients. Because of recording problems in two procedures, we could only analyse and calculate the LVEDA, LVESA and FAC in detail in one patient. Global intra-operative analysis of changes in the left ventricular wall motion was possible in all three procedures and revealed the same trend in LVWMSi. Table 3 presents the time course of changes in LVEDA, LVESA and FAC in one patient and of the changes in LVWMSi in all three patients.

SVRi increased by 87% with simultaneous occlusion of the aorta and vena cava. At the end of the HAP phase, although SNP was given, a further increase by 98% was measured (Table 2, HAPb) and this immediately affected left ventricular filling. LVESA increased by 68% after 2 min, and LVEDA increased by 49% after 5 min (Table 3). PAWP increased by 73% at the end of the perfusion phase (Table 2, HAPb). Although the CI initially decreased in the patient who did not need an i.v. SNP infusion (by 50% at the start of the HAP phase) the overall CI of all the patients did not decrease significantly during the HAP phase (Table 2).

Immediately after opening both vessels, SVRi decreased by 35% compared with the baseline value, and by 67% compared with the value measured at the end of the HAP phase (Table 2, SS, HAPb, AR). Although left ventricular filling and left ventricular wall motion returned immediately to their steady state value in response to this decrease (Table 3), PAWP did not return to its baseline value until the end of the procedure (Table 2). CI increased by 100%, stroke

Table 2 Cardiovascular measurements during the procedure. Values are mean (SD) *$P<0.05$ compared with the value at SS

Parameter	SS	LS	HAPa	HAPb	AR	CR	EO
CI (litre min^{-1} m^2)	2.7 (0.9)	2.4 (0.6)	2.3 (1.1)	2.5 (0.5)	5.5 (2.2)*	4.3 (1.4)*	2.9 (0.7)
PAWP (mm Hg)	11 (3)	14 (4)*	16 (7)	19 (5)*	18 (8)*	15 (6)*	14 (3)
SI (ml m^{-2})	40 (21)	34 (6.7)	31 (13)	28 (11)	57 (22)*	50 (18)*	38 (6.4)
SVRi (dyne s cm^{-5} m^2)	1849 (656)	2244 (811)	3450 (1152)*	3662 (959)*	1196 (384)*	1257 (414)*	1745 (675)
PVRi (dyne s cm^{-5} m^2)	279 (111)	230 (67.8)	256 (131)	200 (152)	148 (110)*	223 (67.9)*	222 (40.8)
LVSWi (g m m^{-2} $beat^{-1}$)	32 (13)	30 (10)	38 (24)	39 (12)	56 (23)*	42 (19)*	34(15)
RVSWi (g m m^{-2} $beat^{-1}$)	3.8 (3.5)	2.9 (2.6)	4.2 (3.8)	3.1 (2.5)	9.1 (5.6)*	8.3 (5.2)*	3.6 (2.6)

Table 3 TOE values measured during the procedure HAPI=within 8 min after starting the hypoxic abdominal perfusion phase, HAPII=within 8 min before the end of the hypoxic abdominal perfusion phase

	SS	LS	HAP1	HAP2	HAP3	HAP4	HAP5	HAPI	HAPII	AR	CR
Patient 1											
LVEDA (cm^2)	8.2	8.4	9.0	10.5	10.7	11.4	12.2		13.4	9.1	7.5
LVESA (cm^2)	3.7	4.6	4.8	6.2	6.1	6.7	7.0		8.1	3.6	3.7
FAC (%)	54	45	47	41	43	41	43		39	60	51
LVWMSi	1	1.9	1.6	1.3	1.8	1.8	1.8		1.5	1	1
Patient 2											
LVWMSi	1.1	1.6						1.8	1.4	1.1	1
Patient 3											
LVWMSi	1	1.4						2.5	2	1.1	1

index, and left and right ventricular stroke work indices also increased at this stage (Table 2). Simultaneously, pulmonary vascular resistance index decreased by 50%.

Discussion

We found that the additional occlusion of the vena cava had only a small stabilizing effect on haemodynamics when the thoracic aorta was occluded. Although RAP, mPAP, CI, SI, LVSWi and RVSWi were stable during simultaneous occlusion of the aorta and vena cava (HAP phase), large changes in important variables such as MAP, FAC and LVWMSi, followed by an increased PAWP, required infusion of SNP in six patients to control these changes. Although SNP infusion was stopped at least 4 min before abdominal reperfusion, opening of both vessels caused profound cardiovascular changes. MAP decreased by 50%, while CI increased by 100%, pulmonary hypertension developed, LVSWi increased by 75% and RVSWi increased by 147%.

Our data contrast with those of animal studies, which reported the additional vena cava inferior occlusion had a stabilizing effect.[2 3] In mongrel dogs anaesthetized with sodium pentobarbital, systolic left ventricular pressure and superior caval vein flow did not change during simultaneous clamping; and left ventricular end diastolic volume decreased.[2] The decrease in stroke volume was assumed to be caused by reduced preload; no activation of the Frank–Starling mechanism was found.[2] Gelman and colleagues[3] studied simultaneous clamping and declamping in pigs anaesthetized with sodium methohexital followed by enflurane. Their report confirmed the data on clamping measured by Stokland and colleagues,[2] i.e. no significant change in MAP or superior caval vein flow, and reduced CO.

Our data confirm the results of the only published clinical report, which found haemodynamic changes similar to those described during thoracic aortic occlusion alone.[4] However, our methods were different. In the previous study, haemodynamic stability after inflation of the aortic balloon was sought by increasing isoflurane concentration, and by starting i.v. SNP, before the inferior caval vein balloon was inflated.[4] The authors speculated that the stepwise clamping, in which a few minutes elapsed between aortic balloon inflation and inferior caval vein balloon inflation, allows the typical, single thoracic aortic cross-clamping redistribution of blood volume, to occur.[4] In our study, less than 1 min elapsed between thoracic aorta and vena cava inferior occlusion. Nevertheless, we also observed changes comparable with those during single thoracic aortic cross-clamping. This is in contrast to the animal experiments, when occlusion of the cava during aortic cross-clamping resulted in the same flows and pressures whether the aorta and inferior caval vein were occluded simultaneously or at different timepoints.[2] Nevertheless, the authors stated that end diastolic volume, superior vena cava flow and systolic left ventricular pressure were very sensitive to changes in blood volume.[2]

The effects of blood volume expansion on haemodynamic changes, studied by infusing blood in 50-ml volumes into the jugular vein during the simultaneous clamping, was found to depend very much on shunting between the upper and lower part of the body.[2] Anatomical shunts exist via the spinal arteries and veins and via azygos and hemi-azygos veins.

To explain the different results between animal and clinical studies, three differences in the conditions may be considered. First, anatomical and physiological differences between species must be taken into account. A second difference is the method of clamping. The clamps in the animal studies were 'extravascular', while both clinical studies used endovascular occlusion. Because MAP increased during the endovascular occlusion, the outside pressure put on the partly compliant balloons (which are only available with a maximum diameter of 30 mm), will be increased, which might have allowed leakage past these balloons during the HAP phase, and increased shunt between the upper and lower compartment. Extravascular cross-clamping with instruments will prevent leakage past the clamps. A third difference between the animal and the clinical studies is the use of atropine. Both animal studies used atropine in order to avoid reflex bradycardia before simultaneous clamping was started,[2,3] whereas the clinical studies did not.[4] Therapeutic doses of atropine can occasionally dilate cutaneous blood vessels, although the mechanism of this anomalous vascular response is unknown.[10] This dilation of cutaneous vessels could affect shunting.

Our data on occlusion release only partly confirm the results of the previously published clinical report.[4] We obtained more detailed data than the study of Berkenstadt and colleagues, who presented values 1 min and 30 min after declamping.[4] We found significant changes in filling pressures. PAWP remained increased to the end of the procedure in all our patients (Table 2), whereas Berkenstadt and colleagues reported no significant changes in filling pressures during these phases.[4] Another difference was their use of ephedrine and phenylephrine to treat hypotension. We did not treat this response, although we found a significant decrease in MAP and increase in CI and HR.[4]

Two patients in our study developed ventricular ectopic beats, PVC (premature ventricular complex) in bigeminy, after occlusion release. These changes in haemodynamic values and the observed arrhythmia are compatible with a post reperfusion syndrome (PRS). The existence of a PRS is known from studies describing liver transplantation.[11,12] It is characterized by brady-arrhythmia, a decreased MAP, SVR and increased mPAP, PAWP and RAP. From studies on single aortic cross-clamping it is also assumed that splanchnic hypoperfusion releases myocardial-depressant factor(s) from the hypoxic tissues, causing myocardial dysfunction after declamping.[1] A rapid decrease in temperature may contribute to PRS.[11,12] As a result of perfusion of the abdomen with fluid below room temperature, hypothermia develops during the HAP phase. There was, however, no immediate change in blood temperature in the AR phase or the CR phase (Figs 2 and 3).

This less invasive perfusion procedure has been said to avoid significant pain or bleeding and be possible even in frail and debilitated patients.[4,5] These studies reported cardiovascular changes, but neither mentioned changes in cardiac performance.[4,5] We disagree that the procedure is trivial. Six patients in our study needed i.v. SNP to control cardiovascular changes. Cardiac wall motion abnormalities were observed in all the TOE monitored patients, probably as a result of myocardial ischaemia, and these abnormalities did not disappear until occlusion release. The increase in the left and right ventricular stroke work indices remained, accompanied by elevated PAWP. Carrying out perfusion under local anaesthesia, without invasive haemodynamic monitoring, in frail or debilitated patients, seems unwise because of the possible additional cardiac stress caused by awareness. The suggested stabilizing effect of additional vena cava occlusion was small. We therefore conclude that the large circulatory changes during simultaneous occlusion of the thoracic aorta and inferior cava make invasive haemodynamic monitoring necessary.

Acknowledgement

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Comparative effect of paracetamol, NSAIDs or their combination in postoperative pain management: a qualitative review

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Background. Quantitative reviews of postoperative pain management have demonstrated that the number of patients needed to treat for one patient to achieve at least 50% pain relief (NNT) is 2.7 for ibuprofen (400 mg) and 4.6 for paracetamol (1000 mg), both compared with placebo. However, direct comparisons between paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) have not been extensively reviewed. The aims of this review are (i) to compare the analgesic and adverse effects of paracetamol with those of other NSAIDs in postoperative pain, (ii) to compare the effects of combined paracetamol and NSAID with those of either drug alone, and (iii) to discuss whether the adverse effects of NSAIDs in short-term use are justified by their analgesic effects, compared with paracetamol.

Methods. Medline (1966 to January 2001) and the Cochrane Library (January 2001) were used to perform a systematic, qualitative review of postoperative pain studies comparing paracetamol (minimum 1000 mg) with NSAID in a double-blind, randomized manner. A quantitative review was not performed as too many studies of high scientific standard (27 out of 41 valid studies, including all major surgery studies) would have been excluded.

Results. NSAIDs were clearly more effective in dental surgery, whereas the efficacy of NSAIDs and paracetamol seemed without substantial differences in major and orthopaedic surgery, although firm conclusions could not be made because the number of studies was limited. The addition of an NSAID to paracetamol may confer additional analgesic efficacy compared with paracetamol alone, and the limited data available also suggest that paracetamol may enhance analgesia when added to an NSAID, compared with NSAIDs alone.

Conclusion. Paracetamol is a viable alternative to the NSAIDs, especially because of the low incidence of adverse effects, and should be the preferred choice in high-risk patients. It may be appropriate to combine paracetamol with NSAIDs, but future studies are required, especially after major surgery, with specific focus on a potential increase in side-effects from their combined use.

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Keywords: analgesics non-opioid, paracetamol; analgesics anti-inflammatory, non-steroidal; pain, postoperative; analgesics

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The aims of this review are (i) to compare the analgesic and adverse effects of paracetamol with those of other non-steroidal anti-inflammatory drugs (NSAIDs) in postoperative pain, (ii) to compare the effects of paracetamol–NSAID combination with those of either drug alone, and (iii) to discuss whether the adverse effects of NSAIDs in short-term use are justified by their analgesic effects compared with paracetamol. In recent systematic quantitative reviews of postoperative pain management based on placebo-controlled trials, ibuprofen 400 mg was shown to have a number needed to treat (NNT) of 2 7 compared with placebo,[1] whereas paracetamol had an NNT of 4.6.[2] NNT is the number of patients needed to treat for one patient to achieve at least 50% pain relief. However, the

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analgesic effect of NSAIDs *vs* paracetamol assessed in direct comparisons has not been reviewed extensively before.[3–5]

Methods

A systematic review of the literature using Medline (1966 to January 2001) and the Cochrane Library (January 2001) was performed. The search profile included a comprehensive list of pain terms combined with 'paracetamol', 'acetaminophen', 'propacetamol', 'non-steroidal anti-inflammatory drugs (NSAID)' or individual drug names. Additional papers not indexed in the databases mentioned were retrieved by reviewing the reference lists from the published material.

Inclusion criteria were postoperative pain, double-blind design, randomized allocation, studies on man, English language and full journal publication. The statistical method had to be described in the study. Each report meeting the inclusion criteria was read by two of the authors and scored for inclusion and methodological quality using a three-item scale of 1–5.[6] Two of the authors agreed on the scores. Reports described as randomized were given 1 point and an additional point if the method of randomization was described and it was appropriate (table of random numbers, computer-generated coin-tossing). Conversely, 1 point was deducted if the method of randomization was inappropriate (alternative allocation, allocation according to date of birth). One point was given when the study was described as double-blind and an additional point if the method of double-blinding was described and was appropriate (identical placebo, dummy). Again, 1 point was deducted if the blinding was inappropriate. Finally, 1 point was given to studies with a description of withdrawals and dropouts. Studies without randomization and blinding were excluded from the review, so the minimum score of an included trial was 2 and the maximum score 5. The studies did not have to be placebo-controlled as the analgesic effect of paracetamol and NSAIDs compared with placebo has been established.[1 2] Clinical trials comparing paracetamol with NSAIDs [including acetylsalicylic acid (ASA)] were sought, as were studies evaluating paracetamol added to an NSAID against paracetamol or NSAID alone.

The dose of paracetamol had to be a minimum of 1000 mg when given as a single agent, because doses below 1000 mg may be insufficient.[7] However, studies employing lower doses of paracetamol were included when given in combination with another NSAID or when administered to children. A wide range of NSAID doses was included. The medication could be administered at different times, including pre- and postoperatively, and by different routes such as i.v., oral and rectal.

Analgesic efficacy was evaluated by significant differences in standard pain measures and/or consumption of opioids/rescue analgesia.

Results

A detailed description of all the studies is presented in Tables 1–3. The patient numbers in the tables excluded those receiving placebo, as it was the numbers receiving paracetamol and/or NSAIDs that we sought to evaluate. The studies were divided into the following comparisons: paracetamol *vs* NSAIDs (Table 1), paracetamol with NSAIDs *vs* paracetamol (Table 2) and paracetamol with NSAIDs *vs* NSAIDs (Table 3). The tables were subdivided into major and minor surgery. Some of the studies belonged to several categories and are therefore mentioned more than once.

We found a total of 47 double-blind and randomized studies, of which six had to be excluded because of inadequate randomization (consecutive allocation) or inadequate statistical methods.[8–13] Three further studies were excluded from evaluation because they failed to demonstrate statistically significant differences in pain scores or opioid consumption between groups receiving drugs of known analgesic efficacy and placebo controls, thus suggesting that the studies lacked sensitivity.[14–16] However, these studies are presented in the tables as they exhibit no apparent methodological problems and separation from placebo does not indicate ability to demonstrate a difference between active drugs. Several studies without placebo controls were included in the review, but these studies are considered to provide weaker evidence when no significant differences between active drugs were demonstrated.

Methodological quality scores ranged from 2 to 5 for all studies. The median value of quality scores for the positive studies (the studies which showed a difference in analgesic effect) and the negative studies were both 4. No statistical difference was found between the two groups using Mann–Whitney test (P=1.0).

Paracetamol vs NSAIDs

There were a total of 36 studies including 3362 patients undergoing a wide variety of surgical procedures (Table 1).

Major surgery

There were four valid studies in major abdominal and gynaecological surgery[17–20] and one involving laparoscopic cholecystectomy,[21] including a total of 398 patients. In the most robust study,[20] rectal diclofenac 50 mg was superior to rectal paracetamol regarding pain scores, but resulted in an equivalent morphine-sparing effect (36 and 40% respectively). There were no significant differences between paracetamol and NSAIDs in pain scores or postoperative morphine requirement in the other four studies. However, there were problems in these studies. Montgomery and colleagues[17] studied a single rectal dose of diclofenac or paracetamol administered preoperatively and assessed its efficacy over 24 h. However, there were significant differences in age and body mass index between the groups,

Table 1 Paracetamol *vs* NSAIDs in postoperative pain *n* refers to the number of patients involved in the specific comparisons, not total number of patients in the study Analgesic outcome results for paracetamol *vs* NSAID· '↑ = greater effect' means that paracetamol was more effective than NSAID, '→ = same effect' means that paracetamol and NSAID had the same effect; '↓ = less effect' means that paracetamol was less effective than NSAID Analgesic outcome results were quantified when possible (e g VAS scores, rescue medication, PCA) Ordinal scale measures cannot be used for quantitative comparisons. OPS = objective and behavioural pain score; P = paracetamol, S = suppository

Author (quality score)	***n***	**Type of surgery**	**Treatment groups**	**Admini-stration**	**Treatment duration and timing**	**Outcome measures**	**Analgesic outcome: paracetamol *vs* NSAID** **↑ = greater effect** **→ = same effect** **↓ = less effect**	**Opioid requirement or analgesic remedication: paracetamol *vs* NSAID**	**Adverse effects (significant differences)**
Major surgery									
Montgomery *et al*, 1996[17] (4)	40	Elective gynaecological surgery (abdominal)	1 P 1500 mg 2. Diclofenac 100 mg 3. P 1500 mg + diclofenac 100 mg	Supp	Single dose, pre-emptive	1. Pain on deep breathing (VAS) 2 Morphine usage (PCA)	→	→	Not described
Witjes *et al.*, 1992[19] (3)	65	Cholecystectomy	1. Naproxen 500 mg × 2 2. P 1000 mg × 4 3 Placebo	Supp	3 days, pre-emptive	1. Pain score (0–3) 2. Usage of buprenorphine	→ P not different from placebo	→	No statistical evaluation
Varrassi *et al*, 1999[18] (5)	174	Elective hysterectomy (abdominal)	1. Propacetamol 2000 mg 2. Ketorolac 30 mg	i.v	Two doses, first dose at extubation	1 Morphine usage (PCA) 2. Pain intensity (VAS) 3. Pain intensity (1–5) 4 Overall analgesic efficacy (1–5)	→	→	No difference
Cobby *et al*, 1999[20] (4)	44	Elective hysterectomy (abdominal)	1. Diclofenac 50 mg 2 P 1300 mg 3. Placebo	Supp	Three doses, first dose at wound closure	1. Morphine usage (PCA) 2. Pain intensity (VAS) 3. Pain relief (0–10)	↓ VAS 24 h (average) P 39 Diclofenac 18	→	No statistical evaluation
Dahl *et al.*, 1997[15] (4)	66	Elective hysterectomy (abdominal)	1. Ibuprofen 800 mg 2. P 1000 mg 3 Placebo	Oral	Single dose, pre-emptive	1. Pain intensity (VAS) 2. Pain intensity (1–5) 3 Quality of sleep	→ Active drug equal to placebo	→ Active drug equal to placebo	No difference between all groups (nausea or perioperative bleeding)
Owen *et al.*, 1997[21] (4)	75	Laparoscopic cholecystectomy	1. Ibuprofen SR (sustained release) 1600 mg × 1 2. P 1000 mg × 4	Oral	7 days, first dose pre-emptive	1 Pain intensity (0–4) 2. Overall efficacy 3 Quality of sleep	→	→	No difference
Minor surgery									
McQuay *et al*, 1986[22] (4)	120	Elective orthopaedic	1 Ketorolac 5 mg 2. Ketorolac 10 mg 3 Ketorolac 20 mg 4. P 500 mg 5. P 1000 mg	Oral	Single dose, postoperative	1 Pain intensity (0–3) 2 Pain intensity (0–7) 3. Pain intensity (VAS) 4 Pain relief (0–4) 5 Pain relief (VAS)	→ (*vs* ketorolac 10 and 20 mg)	→	More sedation with ketorolac 10 and 20 mg compared with P 500 mg
McQuay *et al.*, 1990[23] (5)	120	Elective orthopaedic	1 Bromfenac 5 mg 2 Bromfenac 10 mg 3. Bromfenac 25 mg 4 P 1000 mg 5 Placebo	Oral	Single dose, postoperative	1 Pain intensity (0–3) 2. Pain intensity (0–7) 3 Pain relief (0–4) 4. Pain relief (VAS)	→ Active drug better than placebo	↓ (*vs* bromfenac 25 mg) Remedication not required. P 37% bromfenac (25 mg) 63% → (*vs* bromfenac 10 mg)	No difference

Table 1 *Continued*

Author (quality score)	*n*	Type of surgery	Treatment groups	Administration	Treatment duration and timing	Outcome measures	Analgesic outcome: paracetamol *vs* NSAID ↑ = greater effect → = same effect ↓ = less effect	Opioid requirement or analgesic remedication: paracetamol *vs* NSAID	Adverse effects (significant differences)
Fletcher *et al*, 1997[24] (5)	30	Disc surgery	1 Propacetamol 2000 mg × 4 2. Ketoprofen 50 mg × 4 3 Ketoprofen 50 mg × 4 + propacetamol 2000 mg × 4 4. Placebo	i v.	48 h, first dose at skin closure	1. Pain intensity at rest and mobilization (VAS) 2 Morphine usage (PCA)	→ (pain at rest) ↓ (pain on movement) Active drug better than placebo	→	No difference
Van Lancker *et al*, 1999[14] (3)	49	Arthroscopy	1 Propacetamol 30 mg kg^{-1} 2. Tenoxicam 0.5 mg kg^{-1} 3. Propacetamol + tenoxicam 4. Placebo	i v.	Single dose, pre-emptive	1 Pain intensity (VAS)	→ Active drug equal to placebo	→ Active drug equal to placebo	No difference
Huang *et al.*, 1986[27] (3)	75	Tubal occlusion in local anaesthesia	1 P 1300 mg 2 Meclofenamate 100 mg 3 Meclofenamate 200 mg 4 Placebo	Oral	Pre-emptive, single dose	1 Pain intensity (1–5)	↓	→	No data
Schachtel *et al*, 1989[25] (4)	73	Episiotomy	1 Ibuprofen 400 mg 2 P 1000 mg 3 Placebo	Oral	Single dose, postoperative	1 Pain intensity (0–3) 2 Pain relief (0–4) 3. Overall evaluation of analgesic efficacy (1–5)	↓ Active drug better than placebo	→	None
Skovlund *et al.*, 1991[26] (4)	30	Episiotomy	1. Naproxen 500 mg 2 P 1000 mg	Oral	Single dose, postoperative	1. Pain intensity (VAS)	→	No data	No statistical evaluation
Derkay *et al*, 1998[16] (3)	94 children	Myringotomy	1 P 10 mg kg^{-1} 2. Ibuprofen 10 mg kg^{-1} 3 Placebo	Oral	Single dose, pre-emptive	1 OPS	→ Active drug equal to placebo	→ Active drug equal to placebo	No difference
Bean-Lijewski and Stinson, 1997[28] (4)	125 children	Myringotomy	1. P 15 mg kg^{-1} 2 Ketorolac 1 mg kg^{-1}	Oral	Single dose, postoperative	1. OPS	→ (3 of 5 assessments and authors' conclusion) ↓ (2 of 5 assessments)	No data	No difference
Baer *et al*, 1992[29] (3)	44 children	Adenoidectomy with or without myringotomy	1. Diclofenac 12.5 mg 2 P 125 mg	Supp	Single dose, pre-emptive	1. Pethidine usage 2 Pain behaviour: crying, anxiety, alertness, breathing	→	↓ No requiring pethidine: P 20 diclofenac 9	No difference (bleeding)
Rømsing *et al*, 2000[30] (5)	48 children	Tonsillectomy	1 Diclofenac 2–3 mg kg^{-1} per 24 h in two doses 2. P 90 mg kg^{-1} per 24 h in four doses	Oral	Multiple doses, first dose day 1 after surgery	1. Pain intensity at rest and at drinking (Poker Chip Tool)	→	No data	Higher incidence in P group. nausea and vomiting
Schmidt *et al*, 2001[33] (4)	80	Tonsillectomy	1 Diclofenac 50 mg 2 P 1000 mg	Supp	Single dose, pre-emptive	1 Pain intensity (VAS)	→	→	Intraoperative blood loss significantly greater in diclofenac group

Table 1 *Continued*

Author (quality score)	*n*	Type of surgery	Treatment groups	Administration	Treatment duration and timing	Outcome measures	Analgesic outcome: paracetamol *vs* NSAID ↑ = greater effect → = same effect ↓ = less effect	Opioid requirement or analgesic remedication: paracetamol *vs* NSAID	Adverse effects (significant differences)
Rusy *et al.*, 1994[31] (2)	50 children	Tonsillectomy with or without adenoidectomy	1. Ketorolac 1 mg kg^{-1} + simulated rectal examination 2 P 35 mg kg^{-1}	Ketorolac i v. P supp	Single dose, pre-emptive	1 OPS	→ (serum concentrations of P were below anti-pyretic level)	→	Significantly more blood loss and need for additional haemostasis measures in ketorolac group
Watcha *et al.*, 1992[32] (2)	61 children	Bilateral myringotomy	1. P 10 mg kg^{-1} 2. Ketorolac 1 mg kg^{-1} 3 Placebo (postoperative pain treated with P 15–20 mg kg^{-1} given as supp)	Oral	Single dose, pre-emptive	1 OPS	↓ OPS score· P 4 Ketorolac 1 P equal to placebo	No comparison made between P and ketorolac	No difference
Cooper *et al*, 1989[34] (5)	120	Dental	1 Ibuprofen 400 mg 2 P 1000 mg 3. Placebo	Oral	Single dose, pre-emptive	1. Pain intensity (0–3) 2. Pain relief (0–4) 3. Pain half gone 4 Overall evaluation of analgesic efficacy (0–4)	↓ % very good or excellent overall impression P 27% Ibuprofen 52% Active drug better than placebo	→	More drowsiness in P group
Cooper *et al.*, 1998[42] (4)	151	Dental	1 Ketoprofen 100 mg 2. Ketoprofen 25 mg 3. P 1000 mg 4 Placebo	Oral	Single dose, postoperative	1. Pain intensity (0–3) 2 Pain intensity (VAS) 3. Pain relief (0–4)	→ (*vs* ketoprofen 100 mg) ↑ (*vs* ketoprofen 25 mg) Active drug better than placebo	→	No difference
Dionne, 1986[35] (2)	20	Dental	1 Flurbiprofen 50 mg 2 P 1000 mg	Oral	2 doses, pre-emptive and 4 h postoperative	1 Pain intensity (0–3) 2. Pain intensity (VAS) 3 Global evaluation	↓ (0–4 h) VAS summed P 88 25 flurbiprofen 46 95 → (4–8 h)	No data	No difference
Irvine *et al*, 1982[43] (3)	33	Dental	1 Diflunisal 500 mg 2. P 1000 mg	Oral	1 5 days, first dose postoperative	1 Pain intensity (0–4) 2. Assessment of analgesic efficacy (0–4)	→	No data	None
Kiersch *et al.*, 1994[36] (5)	181	Dental	1 Naproxen sodium 440 mg 2. P 1000 mg 3 Placebo	Oral	Single dose, postoperative	1 Pain intensity (0–3) 2. Pain intensity (VAS) 3. Pain relief (0–4) 4. Pain half gone 5 Overall efficacy (0–4)	↓ VAS summed pain intensity difference 6 h. P 41.5 Naproxen sodium 127 5 Active drug better than placebo	↓ (time to remedication)	No difference
McGaw *et al*, 1987[37] (4)	84 children	Dental	1 aluminium ibuprofen 200 mg 2. P 240–360 mg related to weight 3 Placebo	Oral	Single dose, postoperative	1 Pain intensity (1–4) 2. Pain relief (1–5) 3 Global rating (1–5)	↓ P equal to placebo	No data	Too few for statistical analysis

Table 1 *Continued*

Author (quality score)	***n***	**Type of surgery**	**Treatment groups**	**Admini-stration**	**Treatment duration and timing**	**Outcome measures**	**Analgesic outcome: paracetamol *vs* NSAID ↑ = greater effect → = same effect ↓ = less effect**	**Opioid requirement or analgesic remedication: paracetamol *vs* NSAID**	**Adverse effects (significant differences)**
Mehlisch *et al*, 1984[47] (4)	107	Dental	1. Aspirin 650 mg 2 P 1000 mg 3 Placebo	Oral	Single dose, postoperative	1 Pain intensity (0–3) 2. Pain relief (0–4) 3. Pain half gone 4 Overall efficacy (1–5)	↑ Active drug better than placebo	→	No data
Mehlisch *et al*, 1990[38] (5)	612	Dental	1. Ibuprofen 400 mg 2 P 1000 mg 3. Placebo	Oral	Single dose, postoperative	1 Pain intensity (1–4) 2 Pain relief (1–4)	↓ Active drug better than placebo	↓ Remedication· P 57% ibuprofen 41%	No difference
Mehlisch *et al.*, 1995[39] (5)	200	Dental	1 Ibuprofen 400 mg 2 P 1000 mg 3 Placebo	Oral	Single dose, postoperative	1. Pain intensity (0–3) 2. Pain relief (0–4) 3 Global assessment (0–4)	↓ Active drug better than placebo	↓ Remedication P 60% ibuprofen 26%	No difference
Moore *et al.*, 1985[49] (3)	25 children	Dental	1 Aluminium ibuprofen 200 mg 2. P 240–360 mg related to weight 3 Placebo	Oral	Single dose, postoperative	1. Pain intensity (1–4) 2 Pain relief (1–5) 3. Overall efficacy (1–5)	No comparison made between P and ibuprofen	No comparison made between P and ibuprofen	None
Nystrom *et al.*, 1988[40] (4)	88	Dental	1 Diflunisal 500 mg × 1 2 P 1000 mg × 2	Oral	Single and 2 doses, first dose postoperative	1. Pain intensity (VAS)	↓ Pain reduction. P 36% diflunisal 63%	→	No difference
Olstad *et al*, 1986[41] (3)	24	Dental	1 Indoprofen 400 mg × 2 2. P 1000 mg × 4	Oral	3 days, first dose postoperative	1 Pain intensity (VAS)	↓	No data	Significant increase in bleeding on postoperative days 3, 4 and 5 in indoprofen group (minimal)
Rodrigo *et al*, 1989[44] (3)	32	Dental	1. Diflunisal 500 mg × 1 2 P 1000 mg × 2	Oral	Single and 2 doses, first dose preoperative	1 Pain intensity (VAS)	→	No remedication	None
Seymour *et al*, 1996[45] (4)	124	Dental	1 Ketoprofen 12.5 mg 2. Ketoprofen 25 mg 3. P 1000 mg 4 Placebo	Oral	Single dose, postoperative	1. Pain intensity (VAS) 2 Global assessment (1–5)	→ Active drug better than placebo	→	None
Breivik *et al.*, 1999[48] (5)	68	Dental	1. Diclofenac 100 mg 2 P 1000 mg 3. Diclofenac 100 mg + P 1000 mg	Oral	Single dose, postoperative	1 Pain intensity (VAS) 2 Pain relief (0–4) 3. Overall effect (1–4)	↑ (0.5–3 h) → (0.5–8 h)	→	No difference
Cheung *et al.*, 1992[46] (3)	30	Dental	1 Tenoxicam 40 mg 2 P 1000 mg	Oral	Single dose, pre-emptive	1 Pain intensity (VAS)	→	→	Too few for statistical analysis

which could have affected the opioid requirements. Witjes and colleagues[19] used a relatively insensitive four-point pain scale and consumption of buprenorphine tablets as efficacy measures and found no differences in pain scores between active medication and placebo, but a reduction (P=0.048) in opioid consumption on the day of surgery (consumption of buprenorphine tablets: placebo group 2.3, paracetamol group 1.5, naproxen group 1.8). There were no differences between NSAIDs, paracetamol and placebo on the subsequent 2 days, suggesting low study sensitivity. Out of the three best studies,[18 20 21] only one had a placebo control[20] and therefore proven sensitivity. In this study,[20] diclofenac was superior to paracetamol regarding pain scores. The two other studies[18 21] showed no significant difference in pain scores and none of the three studies showed differences in opioid requirement. In three studies,[17 19 20] paracetamol was administered rectally, which may give lower bioavailability.[3] High bioavailability of paracetamol was present in two out of the three best studies, as paracetamol was administered orally in the study of Owen and colleagues[21] and i.v. in the study of Varrassi and colleagues.[18] In these studies, there were no significant differences in pain scores or opioid consumption between paracetamol and NSAIDs. In summary, the limited number of studies with an optimal design precludes firm conclusions about a potential difference in analgesic effect between paracetamol and NSAIDs in major abdominal surgery. So far, the studies failed to show a substantial difference in analgesic efficacy between paracetamol and NSAIDs.

Orthopaedic surgery

Three trials including 270 orthopaedic patients were analysed.[22–24] None showed any differences in pain scores at rest. However, in one study evaluating pain on movement after disc surgery, ketoprofen was superior.[24] In two robust studies with proven sensitivity, both employing 1000 mg oral doses of paracetamol, McQuay and colleagues found lower opioid requirements after bromfenac 25 mg but not 10 mg compared with paracetamol,[23] but no difference when paracetamol was compared with ketorolac 10–20 mg.[22] In summary, three studies have shown that the efficacy of paracetamol was not substantially different from that of NSAIDs, but again the limited number of studies precludes firm conclusions about the potential difference between paracetamol and NSAIDs. Paracetamol was administered orally or i.v. in all studies avoiding the more unpredictable bioavailability associated with the rectal route.

Gynaecological surgery

There were three trials involving a total of 178 patients after episiotomy[25 26] (103 patients) or tubal occlusion[27] (75 patients). In two placebo-controlled studies, ibuprofen (400 mg)[25] and meclofenamate (100 and 200 mg)[27] improved pain scores compared with paracetamol, but no differences in rescue medication were demonstrated. In the third study, which included only 30 patients, paracetamol was equivalent to naproxen 500 mg but the study sensitivity was not proven.[26] In summary, NSAID was superior to paracetamol in two assay-sensitive trials involving two different surgical procedures.

Ear, nose and throat surgery

There were six valid studies that involved a total of 408 children undergoing ear, nose and throat surgery (myringotomy, adenoidectomy, tonsillectomy).[28–33] One study showed ketorolac (1 mg kg^{-1}) to be superior to paracetamol (10 mg kg^{-1})[32] and paracetamol equal to placebo, possibly reflecting the low dose. Four other studies showed that diclofenac[29 30 33] and ketorolac[31] were equivalent to paracetamol concerning objective pain scores and visual analogue scale (VAS) scores. In the study of Bean-Lijewski and Stinson,[28] there was no clear conclusion. In three out of the six studies, no comparison of opioid requirements could be made.[28 30 32] Opioid requirements were lowered by diclofenac in one study[29] but equivalent to paracetamol in two other studies involving diclofenac and ketorolac.[31 33] In a study of tonsillectomy, rectal paracetamol (35 mg kg^{-1}) was equivalent to ketorolac (1 mg kg^{-1}) i.v. despite all serum concentrations of paracetamol being below the antipyretic level.[31] However, even when high doses of oral paracetamol (90 mg kg^{-1} per 24 h) were given to children after tonsillectomy, this did not improve analgesia compared with diclofenac (2–3 mg kg^{-1} per 24 h).[30] Only one of these six studies included a placebo control.[32] There are problems in interpreting these studies because pain rating in children is difficult. Five out of six studies included no placebo control[28–31 33] and could not differentiate between paracetamol and NSAID. In the study with a placebo control, ketorolac was superior to a relatively low dose of paracetamol (10 mg kg^{-1}).[32]

Dental surgery

Of 16 dental studies, eight showed that NSAIDs were superior to paracetamol with respect to pain scores (1329 patients),[34–41] five showed that they were equivalent (370 patients)[42–46] and two that paracetamol 1000 mg was superior to aspirin 650 mg[47] and diclofenac 100 mg.[48] One study was not evaluated as the statistical comparison of paracetamol with NSAIDs was not performed.[49] Of the eight studies in which NSAIDs were superior regarding pain scores, three also showed NSAIDs to be superior regarding remedication (993 patients).[36 38 39] Of the six studies showing no differences in pain scores, study sensitivity was unproven in three[43 44 46] but the other three studies were robust.[42 45 48] In one study, assay sensitivity was inferred because paracetamol plus codeine was superior to paracetamol.[48] In this study, which involved 68 patients, paracetamol 1000 mg and diclofenac 100 mg were equivalent regarding total pain relief and summed pain intensity difference over 8 h but paracetamol was superior to diclofenac in the first 3 h postoperatively (P=0.001). This could be due to slow onset of action of the enteric-coated diclofenac preparation.[48] Cooper and colleagues[42] showed

Table 2 Paracetamol combined with NSAIDs *vs* paracetamol in postoperative pain. *n* refers to the number of patients involved in the specific comparisons, not the total number of patients in the study. Analgesic outcome results for paracetamol and NSAID *vs* paracetamol: '↑ = greater effect' means that the combination was better than paracetamol alone; '→ = same effect' means that the combination had the same effect as paracetamol alone, '↓ = less effect' means that the combination was less effective than paracetamol alone. Analgesic outcome results were quantified when possible (e.g. VAS scores, rescue medication, PCA). Ordinal scale measures cannot be used for quantitative comparisons. P = paracetamol, Supp = suppository

Author (quality score)	***n***	**Type of surgery**	**Treatment groups**	**Administration**	**Treatment duration and timing**	**Outcome measures**	**Analgesic outcome: paracetamol + NSAID *vs* paracetamol** **↑ = greater effect** **→ = same effect** **↓ = less effect**	**Opioid requirement or analgesic remedication. Paracetamol + NSAID *vs* paracetamol**	**Adverse effects (significant differences)**
Major surgery									
Montgomery *et al*, 1996[17] (4)	59	Elective gynaecological surgery (abdominal)	1. P 1500 mg 2. Diclofenac 100 mg 3. P 1500 mg + diclofenac 100 mg	Supp	Single dose, pre-emptive	1. Pain at deep breathing (VAS) 2. Morphine usage (PCA)	→	↑ Morphine use P 44.9 mg P + diclofenac 27.1 mg	Only morphine-related adverse effects
Beck *et al*, 2000[53] (3)	65	Vaginal or abdominal hysterectomy	1. P 20 mg kg^{-1} 2. P 40 mg kg^{-1} 3. Diclofenac 100 mg + P 20 mg kg^{-1}	Supp	Single dose, pre-emptive	1. Morphine usage (PCA) 2. Pain scores (VAS)	→ (compared with both P doses)	→ (compared with both P doses)	Only morphine-related adverse effects
Minor surgery									
Rubin *et al*, 1984[50] (4)	246	Episiotomy	1. P 648 mg and acetylsalicylic acid 648 mg 2. Acetylsalicylic acid 800 mg and caffeine 65 mg 3. P 1000 mg 4. Placebo	Oral	Single dose, postoperative	1. Pain intensity (0–4) 2. Remedication	↑ Active drug better than placebo	→	No difference
Van Lancker *et al*, 1999[14] (3)	74	Arthroscopy	1. Propacetamol 30 mg kg^{-1} 2. Tenoxicam 0.5 mg kg^{-1} 3. Propacetamol 30 mg kg^{-1} + tenoxicam 0.5 mg kg^{-1} 4. Placebo	i.v	Single dose, pre-emptive	1. Pain intensity (VAS)	→ Active drug equal to placebo	→ Active drug equal to placebo	No difference
Mather *et al.*, 1995[51] (2)	80 children	Tonsillectomy	1. P 20 mg kg^{-1} 2. Placebo + morphine 0.1 mg kg^{-1} 3. P 20 mg kg^{-1} + ketorolac 0.5 mg kg^{-1}	Oral	Single dose, pre-emptive	1. Morphine usage only; no pain scores		↑ No. of patients requiring extra morphine. P9 P + ketorolac 1	Greater incidence of vomiting in morphine group
Fletcher *et al*, 1997[24] (5)	45	Disc surgery	1. Propacetamol 2000 mg × 4 2. Ketoprofen 50 mg × 4 3. Ketoprofen 50 mg × 4 + propacetamol 2000 mg × 4 4. Placebo	i.v.	48 h, first dose at skin closure	1. Pain intensity at rest and mobilization (VAS) 2. Morphine usage (PCA)	↑ (at rest) ↑ (on movement) Active drug better than placebo	↑ Morphine requirement: propacetamol 43.4 mg propacetamol + ketoprofen 23.4 mg	No difference

Table 2 *Continued*

Author (quality score)	***n***	**Type of surgery**	**Treatment groups**	**Administration**	**Treatment duration and timing**	**Outcome measures**	**Analgesic outcome: paracetamol + NSAID *vs* paracetamol ↑ = greater effect → = same effect ↓ = less effect**	**Opioid requirement or analgesic remedication. Paracetamol + NSAID *vs* paracetamol**	**Adverse effects (significant differences)**
Aubrun *et al.*, 2000[52] (3)	50	Spinal fusion surgery	1 Propacetamol 2000 mg × 4 2. Ketoprofen 100 mg × 3 and propacetamol 2000 mg × 4	i.v	24 h, first dose at skin closure	1. Pain intensity (VAS) 2 Pain relief (VAS) 3 Morphine usage (PCA)	↑ (for pain intensity) → (for pain relief)	↑ (during PCA) Total morphine consumption. propacetamol 49 mg propacetamol + ketoprofen 33 mg	No difference
Breivik *et al*, 1999[48] (5)	68	Dental	1 Diclofenac 100 mg 2 P 1000 mg 3. Diclofenac 100 mg and P 1000 mg	Oral	Single dose, postoperative	1 Pain intensity (VAS) 2 Pain relief (0–4) 3 Overall effect (1–4)	↑ Mean VAS (8 h)· P 37 P + diclofenac 19	↑	No difference

paracetamol 1000 mg to be equivalent to ketoprofen 100 mg and superior to ketoprofen 25 mg. Seymour and colleagues[45] showed equivalence between paracetamol 1000 mg and ketoprofen 25 mg but did not examine a higher dose. In these three studies,[42 45 48] there were also no differences in opioid requirements. In all dental studies the medication was given orally, thus making bioavailability comparable. In summary, NSAIDs seem to be superior to paracetamol in dental surgery, regarding both pain scores and remedication. Most of the studies in dental surgery were robust, with relatively sensitive pain measurement scales, adult patients and medication administered orally.

Summary

Out of 33 valid studies, three (all dental studies) showed that the NSAID was superior to paracetamol with respect to both pain scores and opioid requirement or remedication,[36 38 39] two studies showed that NSAIDs reduced opioid requirement or remedication only compared with paracetamol,[23 29] and 10 studies showed that analgesia was improved by NSAIDs compared with paracetamol regarding pain scores, but either did not report opioid requirement or remedication[32 35 37 41] or found no differences.[20 24 25 27 34 40] Sixteen studies showed no differences between paracetamol and NSAIDs in pain scores,[17–19 21–23 26 29–31 33 42–46] and 10 of these studies also showed no differences in opioid requirement or remedication.[17–19 21 22 31 33 42 45 46] Five of these 16 studies[19 22 23 42 45] showed significant differences between active drugs and placebo, strengthening their conclusion of no difference between NSAID and paracetamol. Two studies found paracetamol to be superior to NSAID regarding pain scores, but not remedication requirement.[47 48] One study had an unclear conclusion[28] and one study made no statistical comparison between paracetamol and NSAIDs.[49]

The efficacies of paracetamol and NSAIDs may depend on the type of surgery. Of the three best studies in major abdominal/gynaecological surgery (including laparoscopic cholecystectomy), two found no significant differences between paracetamol and NSAIDs[18 21] and one demonstrated that NSAIDs were superior[20] as regards pain scores. In all three studies, no significant difference was found in opioid requirement. However, there are several methodological problems in these studies and thus no clear conclusion can be made regarding the efficacy of NSAIDs and paracetamol in major surgery. In orthopaedic surgery, three robust studies showed that the efficacy of paracetamol was comparable to that of NSAIDs,[22–24] but more data are needed to allow final conclusions. In gynaecological minor surgery (episiotomy and laparoscopic tubal ligation), no clear conclusion could be made, but NSAIDs seemed to be more efficacious in two assay-sensitive studies. In ear, nose and throat surgery, no clear conclusion could be made but paracetamol and NSAIDs seemed equivalent. In dental

Table 3 Paracetamol combined with NSAIDs *vs* NSAIDs in postoperative pain *n* refers to the number of patients involved in the specific comparisons, not total number of patients in the study. Analgesic outcome results for paracetamol and NSAID *vs* NSAID: '↑ = greater effect' means that the combination was better than NSAID alone, '→ = same effect' means that the combination had the same effect as NSAID alone; '↓ = less effect' means that the combination was less effective than NSAID alone Analgesic outcome results were quantified when possible (e.g VAS scores, rescue medication, PCA) Ordinal scale measures cannot be used for quantitative comparisons. P = paracetamol; Supp = suppository

Author (quality score)	***n***	**Type of surgery**	**Treatment groups**	**Administration**	**Treatment duration and timing**	**Outcome measures**	**Analgesic outcome: P + NSAID *vs* NSAID ↑ = greater effect → = same effect ↓ = less effect**	**Opioid requirement or analgesic remedication. P + NSAID *vs* NSAID**	**Adverse effects (significant differences)**
Major surgery									
Montgomery *et al.*, 1996[17] (4)	59	Elective gynaecological surgery (abdominal)	1 P 1500 mg 2. Diclofenac 100 mg 3. P 1500 mg + diclofenac 100 mg	Supp	Single dose, pre-emptive	1 Pain at deep breathing (VAS) 2. Morphine usage (PCA)	→	→	Only morphine-related side-effects
Minor surgery									
Van Lancker *et al*, 1999[14] (3)	74	Arthroscopy	1. Propacetamol 30 mg kg^{-1} 2 Tenoxicam 0 5 mg kg^{-1} 3 Propacetamol 30 mg kg^{-1} + tenoxicam 0.5 mg kg^{-1} 4. Placebo	i v	Single dose, pre-emptive	1 Pain intensity (VAS)	→ Active drug equal to placebo	→ Active drug equal to placebo	No difference
Fletcher *et al.*, 1997[24] (5)	45	Disc surgery	1 Propacetamol 2000 mg × 4 2. Ketoprofen 50 mg × 4 3 Ketoprofen 50 mg + propacetamol 2000 mg × 4 4 Placebo	i.v	48 h, first dose at skin closure	1 Pain intensity at rest and mobilization (VAS) 2. Morphine usage (PCA)	↑ (at rest) ↑ (on movement) Active drug better than placebo	→	No difference
Breivik *et al.*, 1999[48] (5)	68	Dental	1. Diclofenac 100 mg 2. P 1000 mg 3 Diclofenac 100 mg + P 1000 mg	Oral	Single dose, postoperative	1. Pain intensity (VAS) 2. Pain relief (0–4) 3 Overall effect (1–4)	↑ Mean VAS (8 h) diclofenac 38 P + diclofenac 19	↑	No difference
Matthews *et al*, 1984[54] (4)	18	Dental	1 Diclofenac sodium 50 mg × 2 2 Diclofenac sodium 50 mg × 2 + P 500 mg × 2 3. P 500 mg × 2 4 Placebo	Oral	Two doses, first dose immediately postoperative	1 Pain intensity (VAS)	→ P equal to placebo	→	None

surgery, NSAIDs seemed to be superior to paracetamol regarding pain scores and remedication requirements.

Thus, overall, NSAIDs seem to be superior to paracetamol in postoperative pain management, but the magnitude of the difference may depend on the type of surgery performed. In major surgery, the efficacies of NSAIDs and paracetamol seem to be comparable, whereas in minor surgery NSAIDs seem to be superior.

The combination of paracetamol and NSAID vs paracetamol alone

There was a total of eight studies, out of which seven could be included.[17 24 48 50–53] These involved 613 patients (Table 2). The last study failed to separate active drugs from placebo.[14] Each study involved a different surgical procedure, making comparisons difficult. In four of the studies,[24 48 50 52] the combinations of paracetamol with ASA, of paracetamol with ketoprofen 50 and 100 mg and of paracetamol with diclofenac were associated with lower pain scores than paracetamol alone. In the study of paracetamol and ketoprofen, the combination reduced pain scores both at rest and on movement after disc surgery compared with paracetamol alone.[24] In a study involving spinal fusion surgery,[52] the combination of propacetamol and ketoprofen 100 mg improved pain scores assessed by VAS pain intensity differences. Pain relief scores, on the other hand, were not significantly different between the two groups in this study. In two studies involving major gynaecological surgery,[17 53] there were no differences in pain scores and in one study[51] the pain scores were not measured.

In their assessment of opioid consumption, five out of the seven studies[17 24 48 51 52] reported significant reductions, ranging from 33–46%, when both drugs were used compared with paracetamol alone. However, in one of the studies these findings may have been exaggerated by the low dose of paracetamol and demographic differences between the study groups, as discussed above.[17] In the study involving spinal fusion surgery,[52] the combination of propacetamol and ketoprofen reduced consumption of morphine under patient-controlled analgesia (PCA). In only one of the seven studies was there no advantage in adding an NSAID to paracetamol.[53] This study compared high-dose rectal paracetamol (40 mg kg^{-1}) with diclofenac 100 mg added to paracetamol (20 mg kg^{-1}) and with paracetamol (20 mg kg^{-1}) alone. The lack of difference between a low dose of paracetamol (20 mg kg^{-1}) and its combination with a full dose of an NSAID may suggest low study sensitivity.

In summary, the addition of an NSAID to paracetamol seems to provide additional analgesic efficacy. However, whether this additional analgesic efficacy is a result of a true additive effect or a reflection of NSAIDs being more effective than paracetamol is not clear.

Paracetamol combined with NSAID vs NSAID alone

A total of five studies were found (Table 3), but only four of them, involving 190 patients, were included in our evaluation.[17 24 48 54] One study was excluded because of failure to separate active drugs from placebo.[14] In the most robust trial, the combination of propacetamol with ketoprofen 50 mg reduced pain scores at rest and on movement compared with ketoprofen alone after disc surgery, but there was no associated reduction in opioid requirement.[24] Oral diclofenac 100 mg combined with paracetamol 1000 mg reduced pain intensity scores, improved pain relief scores and reduced the need for rescue analgesia compared with diclofenac alone after dental surgery,[48] though this finding in part reflects the slow onset of an enteric-coated preparation. A dental surgery study[54] found no differences between the combination of diclofenac with paracetamol and diclofenac alone, but the doses of diclofenac and paracetamol were only 50 and 500 mg respectively. In the remaining study, which involved elective gynaecological surgery,[17] there were no significant differences between diclofenac alone and its combination with paracetamol in either pain scores or opioid requirement. However, this study[17] has weaknesses because of differences in age and body mass index, as discussed above.

In summary, the available data are sparse but two trials suggest that standard doses of paracetamol do enhance analgesic efficacy when added to NSAIDs compared with NSAIDs alone.

Adverse effects of paracetamol vs NSAID

Relatively few studies have compared the adverse effects of NSAIDs and paracetamol, especially in the postoperative period. An exhaustive review of adverse effects is beyond the scope of this article but some important data regarding major adverse effects are presented together with a number of less well-known facts.

Gastrointestinal

Ultrastructural damage to the gastric surface epithelium occurs within minutes after ingestion of NSAIDs and gross endoscopically detectable haemorrhages and erosions in the gastroduodenal epithelium occur within hours.[55] A review of short-term NSAID use concluded that there was no evidence of an increased risk of severe gastrointestinal complications during perioperative (<1 week) NSAID treatment.[56] However, patients with active or previous gastroduodenal ulcer were excluded from most of the studies reviewed, and the risk of severe complications from short-term use of NSAIDs cannot be excluded in these patients.[56] A study by Strom and colleagues,[57] including 10 272 patients, showed that ketorolac was associated with a small increased risk of gastrointestinal bleeding (odds ratio=1.17) when analgesic therapy lasted for 5 or fewer days. However, the risk was significantly greater and clinically important when ketorolac was used in higher doses, in older patients and for more than 5 days.[57] A multicentre study of 875 cases of upper gastrointestinal bleeding, verified by endoscopy, suggested that any use of aspirin for more than a 7-day period increased the risk of bleeding by about seven times, and that diclofenac, indometacin, naproxen and piroxicam were associated with a risk similar to that of aspirin.[58] Paracetamol, propyphenazone and metamizole were not associated with this increased risk.

Allergic

NSAIDs may exacerbate asthma, especially in patients with aspirin-induced asthma.[59] Settipane and colleagues[60] determined the prevalence of cross-reactivity to high-dose paracetamol in 50 aspirin-sensitive asthmatic patients and in 20 non-aspirin-sensitive asthmatic control subjects. The study showed that non-aspirin sensitive asthmatic patients did not react to paracetamol, whereas in aspirin-sensitive patients 16 and 20% developed bronchospasm with paracetamol 1000 and 1500 mg respectively. The reactions were generally mild and easily reversed.

Hepatic

Overdose of paracetamol can occasionally lead to irreversible liver injury that can be lethal.[61] The single adult dose that must be ingested to produce severe liver damage is about 150–250 mg kg^{-1}, corresponding to a plasma concentration equal to or greater than 200 mg $litre^{-1}$.[62] Hepatotoxicity has been reported in chronic alcoholics after ingestion of therapeutic doses of paracetamol.[63] However, paracetamol did not induce adverse effects in the liver in 20 patients with chronic liver disease (six with alcoholic liver disease) who were studied over 2 weeks in a double-blind cross-over design in which the patients were given paracetamol 4000 mg day^{-1} or placebo.[64]

Very rare hepatic injury has been observed for nearly all NSAIDs currently on the market, but diclofenac, sulindac and aspirin may be more commonly associated with liver disease.[65]

Renal

Prostaglandins have little influence on renal blood flow (RBF) or glomerular filtration rate (GFR) in normal healthy individuals[66] but oppose the renal vasoconstriction induced by catecholamines, vasopressin and angiotensin in states such as hypovolaemia, congestive heart failure and cirrhosis with ascites.[67] These conditions also prevail in many postoperative patients, who may have major shifts in fluid compartments as well as activation of the neurohumoral stress response. A recent meta-analysis of the influence of NSAIDs on the postoperative renal function of 183 patients with normal preoperative renal function found significantly reduced sodium and potassium excretion and 21–28% reduction in creatinine clearance on day 1 compared with controls. No significant differences were present on day 2 other than a mean rise in serum creatinine of 15 μmol $litre^{-1}$.[68]

A retrospective cohort study[69] found no evidence of an increased incidence of renal failure among 10 000 patients receiving postoperative ketorolac even in the presence of established risk factors, unless therapy exceeded 5 days, when the risk doubled. These conflicting sources of information are difficult to reconcile, but suggest that the readily demonstrable biochemical and haemodynamic effects do not often progress to an adverse outcome. Paracetamol exerts weaker inhibition of peripheral prostaglandin synthesis than NSAIDs.[70 71] It does produce effects on sodium and water excretion comparable to those of NSAIDs,[71] but not on RBF and GFR,[71] even in the stressed kidney.[72]

Haematological

Most studies comparing the effects of NSAIDs and paracetamol on haemostasis have been performed in tonsillectomy patients. In two studies that involved a total of 1544 children treated with ASA 300–1000 mg or paracetamol 240–1000 mg, post-tonsillectomy haemorrhage was seen in 3.1–3.8% in the ASA group and 0.3–0.5% in the paracetamol group.[73 74] Two studies compared blood loss after preoperative administration of non-ASA NSAIDs (rectal diclofenac 0.65–1.0 mg kg^{-1} or i.v. ketorolac 1 mg kg^{-1}) and paracetamol. Both studies found significantly greater blood loss in patients receiving NSAIDs and significantly longer duration of surgery[33] or a greater number of patients requiring additional measures to obtain haemostasis compared with paracetamol.[31] Other prospective[75 76] and retrospective[77 78] studies have found increased postoperative bleeding in patients receiving perioperative ketorolac for tonsillectomy.

Miscellaneous

NSAIDs have significant inhibitory effects on heterotopic bone formation,[79] whereas the effects on fracture union are debatable.[80] However, similar studies on bone healing are not available for paracetamol.

Aspirin and ibuprofen have been shown to disrupt sleep compared with paracetamol and placebo. Thirty-seven male and female subjects had their sleep pattern recorded one night after ingestion of aspirin 650 mg, paracetamol 650 mg or ibuprofen 400 mg.[81] Aspirin and ibuprofen disrupted sleep by increasing the number of awakenings and the percentage of time spent in stage wake and by decreasing sleep efficiency. Paracetamol did not differ significantly from placebo on any measure of the recorded sleep pattern.

Correspondingly, the normal decrease in nocturnal body temperature was attenuated and melatonin synthesis suppressed after NSAID compared with placebo administration in 75 subjects.[82]

Diclofenac has been shown to alter the pharmacokinetics of active morphine metabolites in patients with postoperative pain.[83] Even though morphine consumption decreased by 20% after diclofenac was administered, the concentration of the active metabolite, morphine-6-glucuronide, was unchanged and a significant reduction in respiratory rate occurred.[83]

Discussion

Paracetamol was found to have analgesic efficacy comparable to that of NSAIDs in many of the studies reviewed, but overall, NSAIDs seem to be superior for postoperative pain management, although there seem to be differences in the efficacies of paracetamol and NSAIDs depending on the type of surgery performed. In major and orthopaedic surgery, the efficacies of NSAIDs and paracetamol seem to be comparable and in dental surgery NSAIDs seem superior.

Paracetamol and NSAIDs (ibuprofen and diclofenac) have been assessed compared with placebo in recent Cochrane systematic reviews.[1 2] Paracetamol 1000 mg had an NNT of 4.6 compared with placebo, ibuprofen 400 mg had an NNT of 2.7 and diclofenac 50 mg an NNT of 2.3.[1 2] In these Cochrane reviews, the NNT differences between paracetamol and NSAIDs were calculated from placebo-controlled studies in which dental studies constituted the majority. However, we cannot be certain whether these findings reflect inherent differences in efficacy between the drugs or differences in the sensitivity of the surgical models to NSAIDs and paracetamol. The NNT values may be misleading in the setting of moderate to major surgery, but the limited number of comparative studies in major surgery precludes final conclusions.

The opioid-sparing effect of NSAIDs has often been used as an analgesic efficacy parameter. However, recent studies have suggested that NSAIDs may reduce morphine requirements by reducing the excretion of the active metabolite, morphine-6-glucuronide. Morphine sparing cannot, therefore, be assumed to result in parallel reductions in opioid-related adverse effects. Fentanyl sparing may be a more appropriate surrogate end-point for future NSAID studies as this drug has minimal renal excretion and inactive metabolites.

The addition of NSAIDs to paracetamol may confer additional analgesic efficacy compared with paracetamol alone. Given the conclusion of the direct comparative studies—that NSAIDs may be more effective than paracetamol—the key question is whether the addition of paracetamol to an NSAID will be worthwhile in patients able to take either medication. Even though few robust data are available, standard doses of paracetamol may enhance analgesic efficacy when added to NSAIDs, compared with NSAIDs alone (two trials). Further evidence of this is seen in non-surgical studies of patients with rheumatoid arthritis, in whom indometacin (150 mg day^{-1}) alone and the combination of indometacin (50 mg day^{-1}) with paracetamol (4 g day^{-1}) had the same analgesic effect, but the combination had fewer and milder side-effects.[84] In two other studies, treatment with a combination of naproxen with paracetamol had a greater analgesic effect than treatment with higher naproxen doses alone.[85 86] A review[87] concerning paracetamol in rheumatoid arthritis suggests that there is increasing evidence that combined paracetamol and NSAID treatment is more effective than treatment with NSAIDs alone. The findings that the combination appears to be more effective than either drug alone may support the suggestion that NSAIDs are not greatly superior to paracetamol.

A formal quantitative review (meta-analysis) was not performed as too many studies of high scientific standard would have had to be discarded if we had used the method introduced by McQuay and Moore to convert different pain scales to a common denominator and thereby make them comparable.[88] The key problem for many quantitative reviews is that a large number of papers must be discarded if they do not use standard scales of pain assessment, use analgesic drug consumption (e.g. PCA), employ pre-emptive techniques or involve local anaesthetic blocks. The next problem may be that the remaining trials are not representative.[89] Of the valid studies in this review, 27 out of 41 (including all major surgery studies) would have had to be discarded if a quantitative review were to have been performed. There are also problems concerning qualitative reviews, as the simple vote-counting method may mislead. It ignores the sample size of the constituent studies, the magnitude of the effect in the studies and the validity of their design even when randomized.[90] Inadequate or unclear randomization can overestimate the treatment effect by 30–41% and non-double-blind conditions can overestimate it by 17%.[6] However, quality scores of the studies in this review had a median value of 4 on a scale of 1–5 and there were no differences in quality scores between studies showing a difference in analgesic effect and those that did not show such a difference.

A further perennial challenge for analgesic studies is the multidimensional and mutually opposed nature of the assessments: as pain improves patients are less likely to request analgesia, yet we seek statistically significant differences in one of these dimensions without attempting to anchor the other Thus, in the study of Owen and colleagues,[21] for example, the difference in pain scores between ibuprofen and paracetamol almost achieved statistical significance in favour of the NSAID (P=0.057) despite 50% lower opioid consumption in these patients, but as conventional levels of significance were not reached in either measure and as there was no placebo control this study was considered to represent weak evidence of equality. Had the opioid administration been fixed in both groups, one might surmise that there would have been a significant difference in pain scores, and thus strong evidence for the superiority of NSAIDs. Despite these problems, we consider that the comparison of paracetamol with NSAID in postoperative pain management is important, especially as the side-effects of these compounds are so different.

The very low apparent risk of paracetamol therapy suggests a highly favourable risk:benefit ratio, which might justify a role for paracetamol as a near-routine postoperative background analgesic. Where the additional analgesic effect of an NSAID is particularly sought, as after relatively minor or ambulatory surgery and when the perceived risks from NSAIDs are low, NSAIDs may be preferred as background analgesic.

There were bioavailability problems, especially in the major surgery and paediatric studies, as paracetamol was administered rectally, making the analgesic effect unpredictable compared with the oral or i.v. route. The pharmacokinetics of paracetamol has been reviewed recently, and the bioavailability of paracetamol given by the rectal route ranged from 24–98%.[3] Serum and saliva concentrations after high-dose rectal and oral paracetamol were studied in postoperative adult patients,[91] and it was concluded that administering paracetamol 2000 mg rectally resulted in serum and saliva concentrations during the first 4 h that never exceeded the minimum effective antipyretic serum concentration.

In conclusion, the existing direct comparative studies show that NSAIDs are more effective than paracetamol in some situations, e.g. dental surgery, but the differences are less obvious after other types of surgery. In many studies, paracetamol was given in insufficient doses or administered rectally, potentially underestimating the efficacy, whereas the reduction in morphine requirements may overestimate the inherent analgesic efficacy of the NSAIDs. Paracetamol is definitely a viable alternative to the NSAIDs, especially because of the lower incidence of adverse effects, and should be the preferred choice in high-risk patients. In the absence of firm data, paracetamol should also be considered instead of NSAIDs for pain management after major or orthopaedic surgery, as few differences in efficacies were found in existing data. After tonsillectomy, paracetamol is also recommended because of less bleeding. It may be appropriate to combine paracetamol with NSAIDs, but future studies are required, especially after major surgery. In such studies, there should also be a specific focus on a potential increase in side-effects from their combined use.

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Rectal and parenteral paracetamol, and paracetamol in combination with NSAIDs, for postoperative analgesia

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Background. We have reviewed the analgesic efficacies of rectal and parenteral paracetamol and tested the evidence for a possible additive analgesic effect of the combination of paracetamol with a non-steroidal anti-inflammatory drug (NSAID) in postoperative pain.

Methods. Randomized controlled trials were evaluated. Outcome measures were pain scores and demand for supplementary analgesia.

Results. Eight studies compared rectal paracetamol with placebo. One study of single-dose administration of rectal paracetamol 40–60 mg kg^{-1} and three studies of repeat dosing with 14–20 mg kg^{-1} showed significant analgesic efficacy, while studies of a single dose of 10–20 mg kg^{-1} were negative. Ten studies compared parenteral paracetamol with placebo and eight studies showed improved pain relief with paracetamol. Of the nine studies comparing paracetamol with a combination of paracetamol and an NSAID, six studies showed improved pain relief for the combination while only two of the six studies comparing an NSAID with a combination of an NSAID and paracetamol showed improved pain relief for the combination.

Conclusions. Considering the few studies available, evidence was found of a clinically relevant analgesic effect of rectal and parenteral paracetamol. Concurrent use of paracetamol and an NSAID was superior to paracetamol alone but no evidence was found of superior analgesic effect of the combination compared with the NSAID alone.

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Paracetamol is frequently used as a non-opioid analgesic in postoperative pain. Its mechanism of action is not fully understood, but it is generally accepted that paracetamol is a centrally acting drug.[1 2] The analgesic effect of paracetamol is probably dependent on the rate and amount of active drug reaching the CNS, where its analgesic effect takes place.[3] Paracetamol is available as oral, rectal and injectable formulations. Reports of analgesic efficacy and adverse effects of oral paracetamol have been the subject of recent systematic reviews,[4–8] but evidence-based estimates of clinical analgesic effects of rectal and parenteral paracetamol in postoperative pain are not available.

When pain relief is insufficient with paracetamol alone, a non-steroidal anti-inflammatory drug (NSAID) may be added in combination. NSAIDs inhibit prostaglandin synthesis in peripheral tissues. Some suggest a peripheral–central synergistic action of NSAIDs that varies depending on the particular NSAID and on the presence of an inflammatory process.[9] Concomitant administration of two analgesics with presumably different mechanisms of action may be more effective than the use of either drug alone and may reduce the need for supplementary analgesics after surgery. The combination of paracetamol and NSAIDs is widely used clinically, but consensus on whether such a combination offers a clinically relevant improvement in analgesia is still lacking.

The aim of this systematic review was, first, to review the analgesic efficacy of rectally or parenterally administered paracetamol for postoperative pain relief, and secondly to test the evidence for a possible additive analgesic effect of the combination of paracetamol and an NSAID compared with either drug alone in postoperative pain.

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Table 1 Comparisons of rectal paracetamol with placebo and different doses of paracetamol. $P<0.05$=significant difference between rectal paracetamol group and placebo group or between groups of different doses of paracetamol; n.s =not significant, –=not evaluated, *calculated from demographic data

Reference	**Quality score**	**Patients: paracetamol/ placebo**	**Study group: paracetamol (mg kg^{-1})**	**When given**	**Type of surgery**	**Effect on: Pain score**	**Consumption of supplementary analgesics**	**Comments**
Elhakim[16]	2	4–11 yr 20/20	10	Once after surgery	Dental	n.s	–	Pain assessed 0.25, 0.5, 1 h after surgery Short observation time
Hein *et al*[19]	4	Adults 70/70	17*	Once after surgery	Termination of pregnancy	n.s	n.s	Pain assessed 0.5, 1, 1.7 h after surgery Analgesic consumption evaluated 1.7 h after surgery Short observation time Low pain score
Korpela *et al.*[17]	4	1–7 yr 30/30/30/30	20	Once before surgery	Various day-case	n.s.	n.s	Pain and analgesic consumption evaluated every 10 min for 2 h, and 24 h after surgery
			40			$P<0.05$	$P<0.05$	$P<0.05$ every 10 min for 2 h and at 24 h
			60			$P<0.05$	$P<0.05$	
Jespersen *et al.*[14]	3	Adults 76/72	14*	4 times a day	Gynaecological laparotomy Hip replacement	–	$P<0.05$	Analgesic consumption evaluated 12, 24, 36, 48, 60 h after surgery and $P<0.05$ at 24, 36, 48, 60 h
Witjes *et al*[15]	3	Adults 32/32	14*	4 times a day	Cholecystectomy	n.s.	$P<0.05$	Pain assessed 24, 48, 72 h after administration Analgesic consumption evaluated 24, 48, 72 h after first administration and $P<0.05$ at 24 h
Cobby *et al*[20]	4	Adults 24/21	20*	After surgery, 8, 16 h	Abdominal hysterectomy	n.s	$P<0.05$	Pain assessed 8, 16, 24 h after surgery Analgesic consumption evaluated 2, 4, 6, 8, 10, 12, 16, 24 h after surgery and $P<0.05$ at 6, 8, 10, 12, 16, 24 h Low pain score
Morton and O'Brien[18]	2	5–13 yr 20/20	15–20	4 times a day	Appendectomy	n.s.	n.s	Pain and analgesic consumption evaluated hourly for 24 h after surgery
Beck *et al*[21]	3	Adults 21/22	20 *vs* 40	Once before surgery	Abdominal and vaginal hysterectomy	n.s.	n.s	Pain and analgesic consumption evaluated every 2 h for 12 h, and 24 h after administration Low pain score

Methods

Randomized controlled trials (RCTs) of rectal or parenteral paracetamol, of comparisons of paracetamol given by different routes and of paracetamol in combination with an NSAID (given by any route) for postoperative analgesia were identified using Medline (1966–2000), Embase (1989–2000) and the Cochrane Library (2000) without language restriction, using the words 'paracetamol', 'acetaminophen', 'propacetamol', 'NSAID', 'non-steroidal anti-inflammatory drug', individual drug names and 'postoperative pain'. We last carried out a search in December 2000. Additional reports were identified from reference lists of retrieved reports. Abstracts or unpublished observations were not considered.

Criteria for inclusion

For the first part of the review, reports were considered if they were (i) comparisons of rectal paracetamol with placebo/no treatment, (ii) comparisons of i.v./i.m. paracetamol (propacetamol) with placebo/no treatment, (iii) comparisons of different doses of rectal or i.v./i.m. paracetamol, or (iv) direct comparisons of the same dose of paracetamol given by different routes. Only trials with postoperative pain as an outcome were considered. For the second part of the review, reports were considered if they were (v) comparisons of a combination of paracetamol and an NSAID with the same dose and route of administration of either drug alone for postoperative analgesia, in order to test the evidence for an additive effect of the combination.

Each report which met the inclusion criteria was read independently by all of the authors to assess adequacy of randomization and blinding and to assess the description of withdrawls.[10] Consensus was achieved subsequently. Reports which were described as randomized were given one point, and a further point if the method of randomization was described and considered adequate (table of random numbers, computer-generated, etc.). If the method of

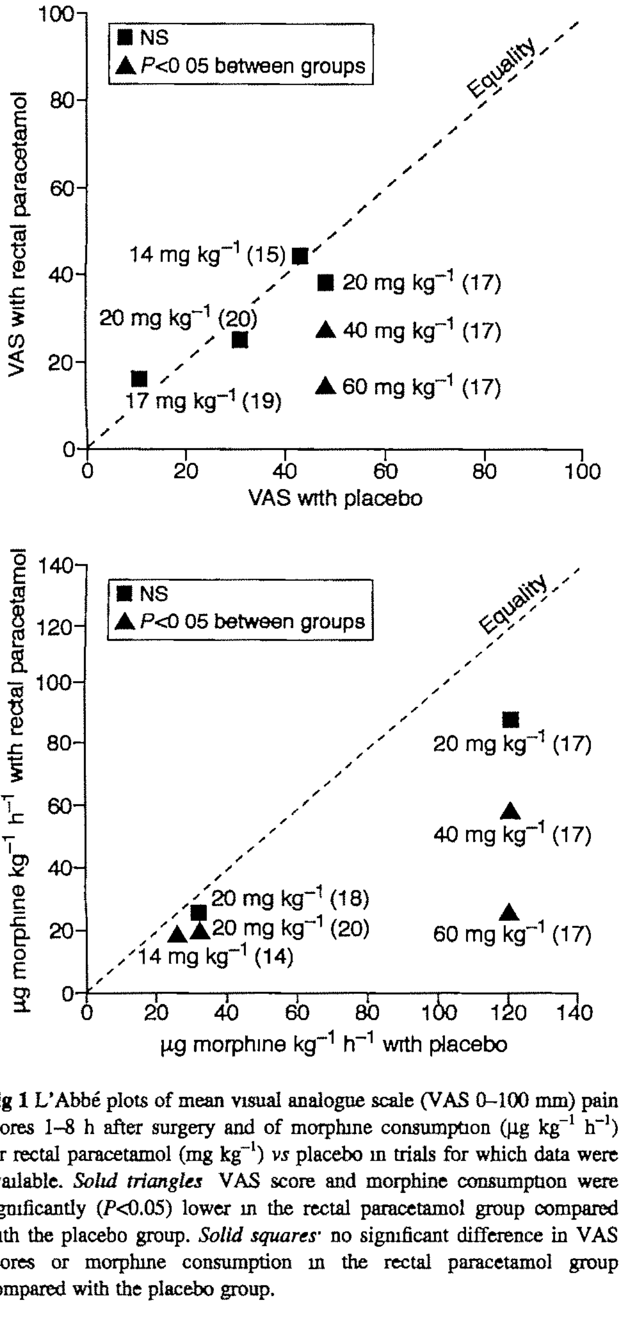

Fig 1 L'Abbé plots of mean visual analogue scale (VAS 0–100 mm) pain scores 1–8 h after surgery and of morphine consumption (μg kg^{-1} h^{-1}) for rectal paracetamol (mg kg^{-1}) *vs* placebo in trials for which data were available. *Solid triangles* VAS score and morphine consumption were significantly (P<0.05) lower in the rectal paracetamol group compared with the placebo group. *Solid squares*: no significant difference in VAS scores or morphine consumption in the rectal paracetamol group compared with the placebo group.

randomization was inappropriate (patients were allocated alternately or according to date of birth, hospital number, etc.) one point was deducted. Reports that were described as double-blind were given one point. If the method of blinding was described and considered appropriate (identical appearance of preparation, double-dummy design, etc.) one additional point was given. If the method of blinding was inappropriate (e.g. comparison of tablet versus injection with no double dummy) one point was deducted. Reports that described the numbers of and reasons for withdrawals were given one point. As there was a prior agreement that reports without randomization would be excluded, the minimum score of an included RCT was 1 and the maximum score was 5. The validity criterion for the inclusion of studies was ≥10 patients per treatment group.[11] Furthermore, scores for intensity of pain were noted. It has been recognized that adequate sensitivity in trials of analgesics for acute pain is only achieved in patients experiencing at least moderate pain [visual analogue scale (VAS) >30 mm] before administration of treatment, since it is difficult to detect an improvement with a low degree of pain or no pain.[12 13]

Data collected

Information about drugs, doses and routes of administration, numbers of patients enrolled and analysed, types of surgery, study design, observation periods, outcome measures and adverse effects was collected on standard collection sheets.

L'Abbé plots of visual analogue scale (VAS) pain scores and of consumption of supplementary morphine were constructed to analyse the degree of pain relief and homogeneity of the data in studies comparing paracetamol with placebo/no treatment and in studies comparing a combination of paracetamol and an NSAID with either drug alone.[11] If the scatter of the individual trials lay predominantly between the line of equality and the control axis, this was taken to indicate efficacy with paracetamol or with the combination of paracetamol and an NSAID and relative homogeneity.

A quantitative analysis was proposed, with calculation of the weighted mean difference (WMD) of VAS scores between treatment groups, taking into account study size and the standard deviations of the VAS scores in the individual trials (using Review Manager software version 3.11; Cochrane Collaboration, Nordic Cochrane Center, Copenhagen, Denmark). Studies using pain scores other than VAS (e.g. verbal rating scale (VRS)) were also included in the quantitative analysis if data could be converted. However, we recognized the possibility that the data would not allow quantitative analysis. Therefore, analgesic efficacy was also evaluated qualitatively by significant difference (P<0.05, as reported in the original investigation) between treatment and control arms in pain intensity using pain scores, consumption of supplementary analgesics and/or time to first analgesic request as outcome measures, and by evaluation of the clinical significance of the differences observed.

Results

A total of 28 trials were identified,[14–41] of which four were subsequently excluded because of duplicate publication[23] and lack of information about randomization.[24 35 36] Data from 24 RCTs, including 37 comparisons involving 2023 patients, of whom 1239 received paracetamol, were analysed. Eight studies compared rectal paracetamol with placebo or different doses of paracetamol,[14–21] 10 compared parenteral paracetamol with placebo,[22 25–33] two compared the

Table 2 Comparisons of parenteral paracetamol (propacetamol) with placebo $P<0.05$=significant difference between parenteral paracetamol group and placebo group, n.s = not significant,–= not evaluated, *calculated from demographic data

Reference	Quality score	Patients: propacetamol/ placebo	Study group: propacetamol (g patient^{-1})	When given	Type of surgery	Effect on: Pain score	Time to first analgesic request	Consumption of supplementary analgesics	Comments
Ang *et al*[25]	2	Adults 20/20	2 (i.m.)	Once after surgery	Orthopaedic	$P<0.05$	$P<0.05$	$P<0.05$	Pain assessed 0.25, 0.5, 1, 2, 3, 4, 5, 6 h after administration and $P<0.05$ at 0.5, 1, 2, 3, 4, 5, 6 h Analgesic consumption evaluated and $P<0.05$ 6 h after administration
Granry *et al*[29]	3	6–13 yr 44/43	1* (i.v.)	Once after surgery	Limb	$P<0.05$	$P<0.05$	–	Pain assessed 0.25, 0.5, 1, 2, 3, 4, 5, 6 h after administration and $P<0.05$ at 1, 2, 3, 4, 5, 6 h
Jarde and Boccard[30]	3	Adults 108/109	2 (i.v.)	Once after surgery	Hallux valgus	$P<0.05$	$P<0.05$	–	Pain assessed 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6 h after administration and $P<0.05$ at 0.5, 0.75, 1, 2, 3, 4, 5, 6 h
Seymour and Rawlins[22]	2	Adults 11/11	2 (i.v.)	Once after surgery	Dental	$P<0.05$	–	–	Pain assessed at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4 h after administration and $P<0.05$ at 1.5, 2, 3, 4 h paracetamol 1 g injection
Farkas *et al*[26]	5	Adults 29/30	2 (i.v.)	Once after surgery	Abdominal aortic repair	$P<0.05$	n.s	–	Pain assessed at 0.5, 1, 2, 3, 4, 5, 6 h after administration and $P<0.05$ at 1, 2, 3 h
Hans *et al*[27]	1	Adults 20/20	2 (i.v.)	4 times a day	Lumbar disc	n.s.	n.s	$P<0.05$	Pain assessed hourly for 14 h after surgery Analgesic consumption evaluated hourly for 14 h, and 24 h after surgery and $P<0.05$ at 6, 7, 8, 9 h
Delbos and Boccard[28]	2	Adults 30/30	2 (i.v.)	4 times a day	Knee ligamento-plasty	n.s	–	$P<0.05$	Pain assessed hourly for 4 h and every 2 h up to 24 h after first administration Analgesic consumption evaluated hourly for 4 h and every 2 h up to 24 h after first administration and $P<0.05$ at 4, 6, 8, 10, 12, 14, 16 h
Peduto *et al.*[32]	5	Adults 42/47	2 (i.v.)	4 times a day	Hip arthroplasty	n.s.	–	$P<0.05$	Pain assessed hourly for 4 h and every 2 h up to 24 h after administration Analgesic consumption evaluated and $P<0.05$ 24 h after administration
Fletcher *et al.*[31]	5	Adults 15/15	2 (i.v.)	4 times a day	Lumbar disc	n.s.	–	n.s.	Pain assessed every 6 h for 48 h after surgery Analgesic consumption evaluated 48 h after surgery
Lancker *et al*[33]	4	Adults 24/25	2* (i.v.)	1 h before surgery, repeated after 6 h	Arthroscopy	n.s.	n.s	n.s	Pain assessed 0.5, 1, 2, 4, 24 h after surgery Analgesic consumption evaluated 4, 24 h after surgery Low pain score

same dose of paracetamol given by different routes,[30 34] nine compared paracetamol with a combination of paracetamol and an NSAID,[18 21 31 33 37–41] and six compared an NSAID with a combination of an NSAID and paracetamol.[18 31 33 38 40 41] The range of numbers of patients included in the studies was 11–217. The median quality score of the studies was 3 (range 1–5). Details of the studies included are shown in Tables 1–5.

Quantitative analysis of VAS pain scores was performed only with reports of i.v. propacetamol. For the other reports (rectal paracetamol and combinations of paracetamol and NSAID), lack of data allowed only qualitative analysis. Instead, any statistical difference between treatments in these reports was extracted from the original investigations and documented in table format, as has been done in other systematic qualitative reviews.[42–44]

Rectal paracetamol versus placebo and different doses of paracetamol

Seven studies with nine treatment arms compared rectal paracetamol with placebo[14–20] and one study with two treatment arms compared two doses of rectal paracetamol[21] (Table 1). In five trials rectal paracetamol was administered before surgery[14 15 17 18 21] and in three trials paracetamol was administered after surgery.[16 19 20] In one study, paracetamol was administered as a rectal solution.[14] Only in three studies was information about the vehicle base of the suppository given.[17 20 21] In all three studies, lipophilic-based paracetamol suppositories were used. Four studies employed a single-dose design[16 17 19 21] and four studies employed a multidose design.[14 15 18 20] The surgery included abdominal, gynaecological and odontological procedures (Table 1).

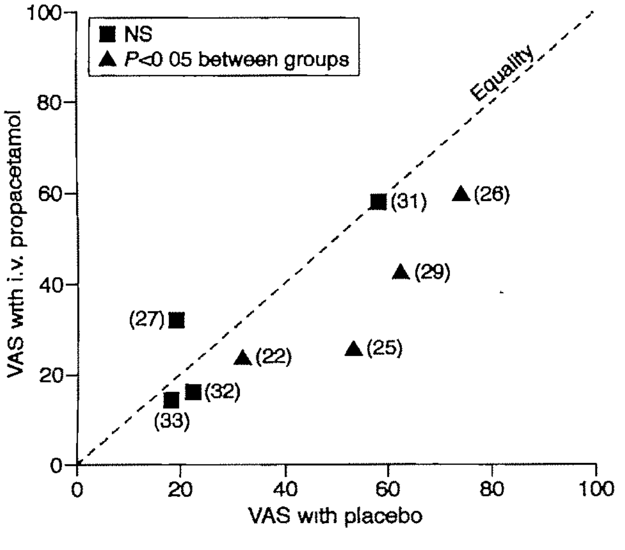

Fig 2 L'Abbé plot of mean VAS score 4–6 h after surgery for parenteral paracetamol (propacetamol) *vs* placebo in trials for which data were available. *Solid triangles*: VAS scores were significantly ($P<0.05$) lower in the parenteral paracetamol group compared with the placebo group. *Solid squares*, no significant difference in VAS scores in the parenteral paracetamol group compared with the placebo group

In three trials of single-dose administration of rectal paracetamol 10–20 mg kg^{-1}, no effect on pain scores or analgesic demand were observed[16 17 19] compared with placebo. However, in the only trial of single-dose administration of rectal paracetamol 40 and 60 mg kg^{-1},[17] pain scores and analgesic demand were significantly reduced in the early postoperative period, by approximately 21–34 mm on a VAS scale and 60–67% respectively. In contrast, no difference between study groups was observed in one trial comparing 20 and 40 mg kg^{-1} [21] (Fig. 1).

In four trials of rectal paracetamol 14–20 mg kg^{-1} four times a day,[14 15 18 20] pain scores were evaluated in three trials[15 18 20] but were not significantly different between study groups in any of the studies (Fig. 1). However, supplementary analgesic consumption evaluated over 24–72 h periods was significantly reduced, by 16–36%, by rectal paracetamol (Fig. 1) in three[14 15 20] of the four repeat dosing studies.[14 15 18 20]

No study evaluated time to first analgesic request.

In three studies, pain scores in the control groups were either low (VAS <30 mm)[19 21] or the observation time was very short.[16 19] Failure to detect analgesic effects of paracetamol may therefore have been the result of lack of sensitivity.[19 21]

Information about adverse effects was provided in seven studies[14–20] and no adverse effects attributable to rectal paracetamol were reported.

In summary, single doses of rectal paracetamol 10–20 mg kg^{-1} did not improve postoperative pain relief. However, single doses of rectal paracetamol 40–60 mg kg^{-1} did, in the only study available, significantly improve postoperative analgesia. Furthermore, in three of four studies, repeat dosing with rectal paracetamol 14–20 mg kg^{-1} was followed by a statistically and clinically significant reduction in analgesic consumption.

Parenteral paracetamol (propacetamol) versus placebo

Ten studies compared i.v.[22 26–33] or i.m.[25] propacetamol 1 or 2 g (corresponding to paracetamol 0.5 g and 1 g respectively) with placebo (Table 2). Paracetamol was administered 1 h before surgery in one study[33] and after surgery in nine studies.[22 25–32] Five studies employed a single-dose design[22 25 26 29 30] and five used a multidose design.[27 28 31–33] The surgical procedures were orthopaedic, abdominal and odontological (Table 2).

Pain scores were significantly lower in five of the 10 studies with parenteral paracetamol,[22 25 26 29 30] with VAS reductions of 9–18 mm up to 4 h[22] and 6 h[29] after surgery (Fig. 2). In two of the studies with no difference in pain scores between treatment groups, patient-controlled morphine was administered as supplementary analgesia.[28 32]

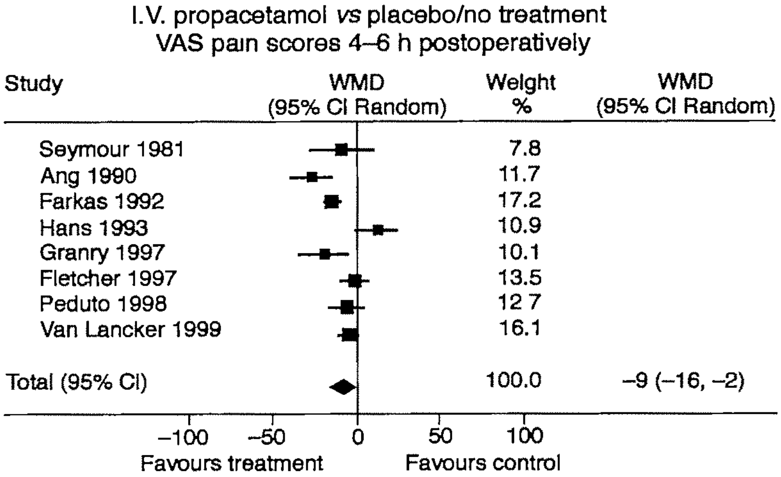

Fig 3 Weighted mean difference (WMD) with 95% confidence intervals (95% CI, horizontal lines) in VAS scores 4–6 h after surgery between the parenteral paracetamol groups and the placebo groups in eight trials. References 26 and 28 were not included in the calculations because of lack of dispersion measures. 'Total' indicates the results of pooling all the trials. Numbers in the column headed 'Weight' indicate the weight of the individual trials in the analysis, taking into account study size and standard deviations of VAS scores

Table 3 Comparisons of paracetamol given by different routes. $P<0.05$=significant difference between groups;–= not evaluated

Reference	Quality score	Patients	Study group: paracetamol	When given	Type of surgery	Effect on: Pain score	Time to first analgesic request	Consumption of supplementary analgesics	Comments
Jarde and Broccard[30]	3	Adults i.v./oral 108/106	1 g	Once after surgery	Hallux valgus	$P<0.05$	$P<0.05$	–	Pain assessed 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6 h after administration and $P<0.05$ at 0.5, 0.75 1, 2, 3, 4 h I.v. administration significantly better than oral
Anderson *et al.*[34]	4	3–15 yr Oral/rectal 50/50	40 mg kg^{-1}	Oral: once 40 min before surgery Rectal: once before surgery	Tonsillectomy	$P<0.05$	–	$P<0.05$	Pain and analgesic consumption evaluated 0.5 h after surgery and $P<0.05$ at 0.5 h Oral administration significantly better than rectal Short observation time

Quantitative analysis of pain scores recorded 4–6 h after surgery was performed using a random effects model, as a test for heterogeneity was significant (P=0.0001). Eight studies were included in the analysis. In the two studies not included, one of which showed a reduced pain score,[30] there was a lack of dispersion measures for the calculation.[28 30] The analysis revealed a statistically significant overall WMD in VAS scores of −9 mm (95% confidence interval −16 to −2 mm) in favour of the parenteral paracetamol groups compared with the placebo groups (Fig. 3).

Time to first analgesic request was evaluated in six studies[25–27 29 30 33] and was significantly increased, by about 38–119 min in the paracetamol groups,[25 29 30] in only three studies.

Supplementary analgesic consumption was evaluated in six studies[25 27 28 31–33] and in four studies[25 27 28 32] it was significantly reduced, by 36–50%, over periods of 6[25] and 24 h[27 28 32] in the paracetamol groups compared with placebo. Adequate sensitivity was not guaranteed in one of the negative studies as VAS pain scores in the control group were less than 30 mm.[33]

Information about adverse effects was provided in eight studies.[25 26 28–33] In two studies, pain during infusion or at the injection site was reported in the propacetamol groups.[29 30]

In summary, of the 10 studies comparing parenteral paracetamol with placebo, eight[22 25–30 32] showed improved pain relief after administration of parenteral propacetamol

Table 4 Comparisons of paracetamol with a combination of paracetamol and an NSAID PCM=paracetamol; $P<0.05$=significant difference between PCM group and PCM plus NSAID group; n s.=not significant;–= not evaluated

Reference	Quality score	Patients: PCM/PCM and NSAID	Study groups:		When given	Type of surgery	Effect on:			Comments
			PCM	NSAID			Pain score	Time to first request for analgesic	Consumption of supplementary analgesics	
Breivik *et al*[41]	5	Adults 24/24	1 g	Diclofenac 100 mg	Once after surgery	Dental	$P<0.05$	$P<0.05$	$P<0.05$	Pain assessed and $P<0.05$ every 0.5 h for 8 h after administration Analgesic consumption evaluated and $P<0.05$ 8 h after administration **Oral administration**
Fletcher *et al*[31]	5	Adults 15/15	1 g	Ketoprofen 50 mg	4 times a day	Lumbar disc	$P<0.05$	–	$P<0.05$	Pain assessed and $P<0.05$ every 6 h for 48 h after surgery Analgesic consumption evaluated and $P<0.05$ 48 h after surgery **I.v. administration** Propacetamol 2 g
Matthews *et al.*[38]	3	Adults 18/18	500 mg	Diclofenac 50 mg	After 6 h surgery	Dental	$P<0.05$	–	n s.	Pain assessed hourly from 3 to 12 h after surgery and $P<0.05$ 3, 4, 7, 8, 9, 10, 11, 12 h Analgesic consumption evaluated 12 h after surgery **Oral administration**
Beck *et al.*[21]	3	Adults 21/22	20 mg kg^{-1}	Diclofenac 100 mg	Once before surgery and vaginal hysterectomy	Abdominal	$P<0.05$	–	n.s	Pain assessed every 2 h for 12 h and 24 h after administration $P<0.05$ at 4 h Analgesic consumption evaluated every 2 h for 12 h and 24 h after administration **Rectal administration** Low pain score
Montgomery *et al*[40]	5	Adults 20/19	1.5 g	Diclofenac 100 mg	Once before surgery	Abdominal gynaecological	n s	–	$P<0.05$	Pain assessed 6, 24 h after surgery Analgesic consumption evaluated and $P<0.05$ 6, 24 h after surgery **Rectal administration**
Mather and Peutrell[39]	2	3–12 yr 24/28	20 mg kg^{-1}	Ketorolac 0.5 mg kg–1	PCM once 1 h before surgery Ketorolac: once before surgery	Tonsillectomy	–	–	$P<0.05$	Analgesic consumption evaluated and $P<0.05$ 24 h after surgery **PCM: oral administration** **Ketorolac.: i.m. administration**
Morton and O'Brien[18]	2	5–13 yr 20/20	15–20 mg kg^{-1}	Diclofenac 1 mg kg^{-1}	PCM 4 times a day and diclofenac 3 times a day	Appendectomy	–	–	n.s.	Analgesic consumption evaluated hourly for 24 h after surgery **Rectal administration**
Fassolt and Stocker[37]	2	Adults 29/29	650 mg	Suprofen 100 mg	Once, day after surgery	Various	n.s	–	n s	Pain assessed 0.5, 1, 2, 3, 4, 5, 6 h after administration Analgesic consumption evaluated 6 h after administration **Oral administration**
Lancker *et al.*[33]	4	Adults 24/25	15 mg kg^{-1}	Tenoxicam 0.5 mg kg^{-1}	PCM. 1 h before surgery, repeated after 6 h Tenoxicam once 1 h before surgery	Arthroscopy	n.s.	n.s	n s	Pain assessed 0.5, 1, 2, 4, 24 h after surgery Analgesic consumption evaluated 4, 24 h after surgery **I.v. administration** Low pain score Propacetamol 30 mg kg^{-1}

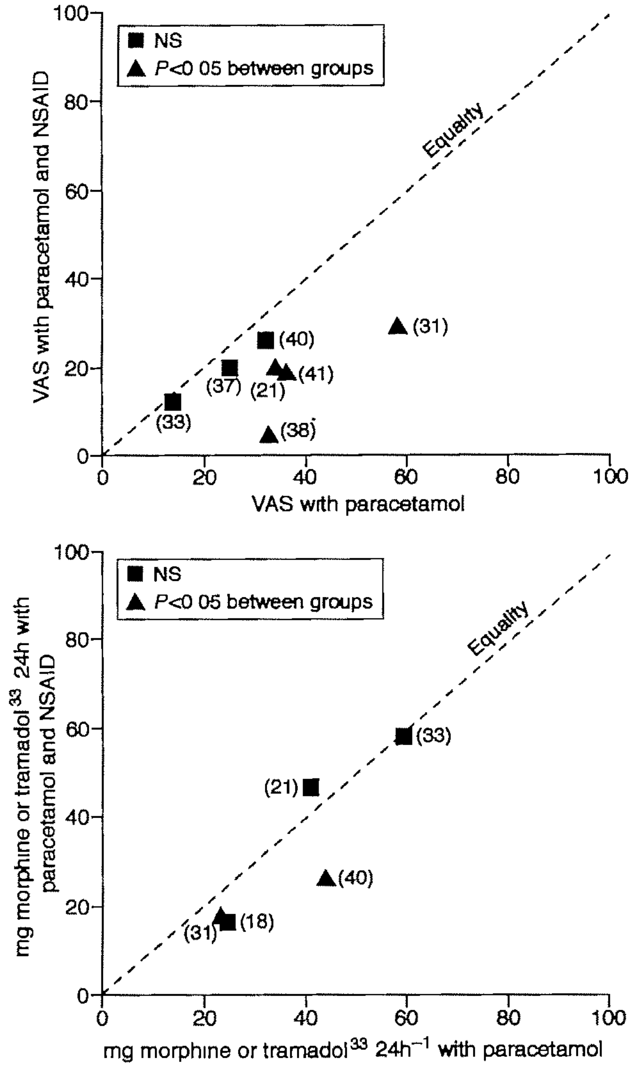

Fig 4 L'Abbé plots of mean/median VAS scores 4–8 h after surgery and of morphine or tramadol consumption (mg per 24 h) for paracetamol *vs* paracetamol and an NSAID in trials for which data were available *Solid triangles*. VAS scores and morphine consumption were significantly ($P<0$ 05) lower in the paracetamol plus NSAID group compared with the paracetamol group. *Solid squares* no significant difference in VAS scores and morphine consumption in the paracetamol plus NSAID group compared with the paracetamol group.

and quantitative analysis was statistically significant in favour of the treatment groups.

Comparisons of paracetamol given by different routes

Two studies compared parenteral with oral paracetamol and oral with rectal paracetamol respectively[30 34] (Table 3). In the comparison of parenteral and oral administration, paracetamol 1 g was given after surgery in each study group. Pain scores were significantly lower up to 4 h after surgery and time to first analgesic request was significantly increased, by 34 min, in the parenteral group[30] (Table 3). In the study comparing oral with rectal administration, 40 mg kg^{-1} of paracetamol elixir or suppositories was given 40 min preoperatively or after induction of anaesthesia respectively[34] (Table 3). In the oral group, there was a significant reduction in pain score at 0.5 h (by approximately 20 mm on the VAS) and in analgesic demand over 4 h (by 57%).[34]

Although results from these studies showed improved pain relief with parenteral compared with oral paracetamol and with oral compared with rectal paracetamol, the data are much too sparse for meaningful conclusions.

Comparisons of paracetamol with a combination of paracetamol and an NSAID

Nine studies compared paracetamol with a combination of paracetamol and an NSAID[18 21 31 33 37–41] (Table 4). Paracetamol 15–20 mg kg^{-1} [18 21 33 39] or 0.5–1.5 g[31 37 38 40 41] was administered in a single-dose[21 37 39–41] or multidose design.[18 31 33 38] The NSAIDs were diclofenac 50–100 mg[21 38 40 41] or 1 mg kg^{-1},[18] ketoprofen 50 mg,[31] ketorolac 0.5 mg kg^{-1},[39] suprofen 100 mg[37] and tenoxicam 0.5 mg kg^{-1},[33] and were given as a single dose[21 33 37 39–41] or repeatedly.[18 31 38] Paracetamol and NSAIDs were administered before surgery in five studies,[18 21 33 39 40] after surgery in three studies[31 38 41] and the day after surgery in one study.[37] Further details of the studies are shown in Table 4. Pain scores were evaluated in seven studies. Four studies[21 31 38 41] showed significantly lower pain scores after administration of the combination of paracetamol and an NSAID compared with paracetamol alone, with VAS reductions of 12–34 mm at 4 h[21] and up to 8,[41] 12[38] and 48 h[31] after surgery (Fig. 4).

Time to first analgesic request was evaluated in only two studies.[33 41] It was increased significantly, by 180 min, in the combination group in one study.[41] In four studies,[31 39–41] supplementary analgesic consumption was significantly reduced, by 34–73% over periods of 8,[41] 24,[39 40] and 48 h[31] in the paracetamol and NSAID groups. In the five other trials, no difference between study groups was observed (Fig. 4).

Two of the negative studies were not considered adequately sensitive as VAS pain scores in the control groups were less than 30 mm.[21 33]

Information about adverse effects was provided in eight studies.[18 31 33 37–41] No adverse effects attributed to the concomitant administration of paracetamol and NSAIDs were reported.

In summary, of the nine studies comparing paracetamol with a combination of paracetamol and an NSAID, six[21 31 38–41] showed improved pain relief after administration of the combination.

Table 5 Comparisons of an NSAID with a combination of an NSAID and paracetamol. PCM=paracetamol; $P<0.05$=significant difference between NSAID group and NSAID and PCM group; n.s =not significant;–=not evaluated

Reference	Quality score	Patients: NSAID/PCM and NSAID	Study groups		When given	Type of surgery	Effect on:			Comments
			PCM	NSAID			Pain score	Time to first request for analgesic	Consumption of supplementary analgesics	
Breivik *et al.*[41]	5	Adults 24/24	1 g	Diclofenac 100 mg	Once after surgery	Dental	$P<0.05$	$P<0.05$	$P<0.05$	Pain assessed and $P<0.05$ every 0.5 h for 8 h after administration Analgesic consumption evaluated and $P<0.05$ 8 h after administration **Oral administration**
Fletcher *et al*[31]	5	Adults 15/15	1 g	Ketoprofen 50 mg	4 times a day	Lumbar disc	$P<0.05$	–	n.s	Pain assessed and $P<0.05$ every 6 h for 48 h after surgery Analgesic consumption evaluated 48 h after surgery **I.v. administration** Propacetamol 2 g
Montgomery *et al*[40]	5	Adults 20/19	1.5 g	Diclofenac 100 mg	Once before surgery	Abdominal gynaecological	n.s	–	n.s.	Pain assessed and analgesic consumption evaluated 6, 24 h after surgery **Rectal administration**
Morton and O'Brien[18]	2	5–13 yr 20/20	15–20 mg kg^{-1}	Diclofenac 1 mg kg^{-1}	PCM 4 times a day and diclofenac 3 times a day	Appendectomy	n.s	–	n.s	Pain and analgesic consumption evaluated hourly for 24 h after surgery **Rectal administration**
Lancker *et al.*[33]	4	Adults 25/25	15 mg kg^{-1}	Tenoxicam 0.5 mg kg^{-1}	PCM 1 h before surgery, repeated after 6 h Tenoxicam: once 1 h before surgery	Arthroscopy	n.s	n.s	n.s	Pain assessed 0.5, 1, 2, 4, 24 h after surgery Analgesic consumption evaluated 4, 24 h after surgery **I.v. administration** Propacetamol 30 mg kg^{-1} Low pain score
Matthews *et al.*[38]	3	Adults 18/18	500 mg	Diclofenac 50 mg	After surgery, 6 h	Dental	n.s.	–	n.s.	Pain assessed hourly 3–12 h after surgery Analgesic consumption evaluated 12 h after surgery **Oral administration**

Comparisons of an NSAID with a combination of an NSAID and paracetamol

Six studies compared an NSAID with a combination of an NSAID and paracetamol[18 31 33 38 40 41] (Table 5). The NSAIDs were diclofenac 50–100 mg[38 40 41] or 1 mg kg^{-1},[18] ketoprofen 50 mg[31] and tenoxicam 0.5 mg kg^{-1},[33] administered as a single dose[33 40 41] or with repeat dosing.[18 31 38] Paracetamol 15–20 mg kg^{-1} [18 33] or 0.5–1.5 g[31 38 40 41] was given as a single dose[40 41] or repeatedly.[18 31 33 38] The NSAIDs and paracetamol were administered before surgery in three studies[18 33 40] and after surgery in three studies.[31 38 41] Further details of the studies are shown in Table 5.

Pain scores were significantly reduced after administration of the combination of the NSAID and paracetamol compared with the NSAID alone in two studies,[31 41] with a VAS reduction of 11–29 mm up to 8[41] and 48 h[31] after surgery. In the four other studies no difference was observed (Fig. 5).

Time to first analgesic request was evaluated in two studies[33 41] but in only one study was it significantly increased (by 150 min) by the combination treatment.[41] In one study, [41] supplementary analgesic consumption

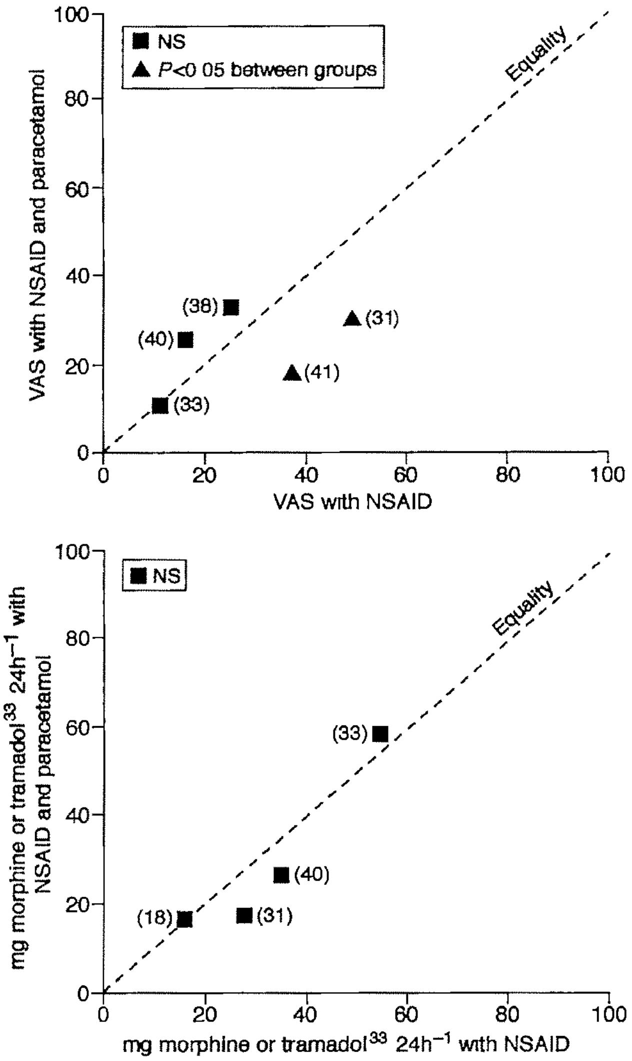

Fig 5 L'Abbé plots of mean/median VAS scores 4–8 h after surgery and of morphine or tramadol consumption (mg per 24 h) for an NSAID *vs* an NSAID and paracetamol in trials for which data were available *Solid triangles*: VAS scores and morphine consumption were significantly ($P<0.05$) lower in the NSAID and paracetamol group compared with the NSAID group *Solid squares* no significant difference in VAS scores and morphine consumption in the NSAID and paracetamol group compared with the NSAID group

was significantly reduced (by 67%) over 8 h in the NSAID plus paracetamol group. In none of the other trials was analgesic demand different between study groups (Fig. 5). One study was not considered adequately sensitive as VAS scores in the control group were less than 30 mm.[33] Information about adverse effects was provided in all six studies[18 31 33 38 40 41] and no adverse effects attributed to the combination of NSAID and paracetamol were reported.

In summary, of the six studies comparing an NSAID with a combination of an NSAID and paracetamol, only two[31 41] showed improved pain relief after administration of the combination.

Discussion

Paracetamol is widely used for the management of perioperative pain. However, except for oral paracetamol, there is a marked discrepancy between the extent to which paracetamol is used and the available evidence for an analgesic effect in postoperative pain.

In order to clear up this discrepancy, we wanted to provide an evidence-based estimate of a clinical analgesic effect of rectal or parenteral paracetamol and of the combination of paracetamol and an NSAID compared with either drug alone in postoperative pain.

Surprisingly few eligible randomized studies were found. It was possible to perform a quantitative analysis of VAS pain scores with studies of parenteral paracetamol. In studies of rectal paracetamol and of combinations of paracetamol and an NSAID, lack of data allowed only a qualitative analysis. To describe data from original trials as thoroughly as possible, L'Abbé plots of VAS pain scores and the consumption of supplementary morphine were constructed.

Rectal paracetamol

There seems to be evidence for a clinically relevant analgesic effect of rectal paracetamol with an opioid-sparing effect comparable with that of NSAIDs. The rather high single doses of 40 and 60 mg kg^{-1} or repeat doses of paracetamol used in the four positive studies[14 15 17 20] are likely to have led to a greater area under the curve for plasma paracetamol concentrations and therefore possibly greater efficacy over the study period than the single (lower) dose methods used in the four negative studies.[16 18 19 21]

The bioavailability of paracetamol suppositories is variable. It is approximately 80% of that of the tablets and the rate of absorption is slower, with maximum plasma concentrations achieved about 2–3 h after administration.[45] This has to be taken into account in the dosing and timing of paracetamol in surgical patients. It is not optimal to administer rectal paracetamol at the induction of anaesthesia in procedures lasting only 0.5–1 h or to administer rectal paracetamol after surgery. Timing may have had an impact on the results in the negative studies. In clinical practice, it has to be taken into consideration that the vehicle base of the suppository has been shown to have an effect on the absorption of poorly soluble drugs such as paracetamol. A lipophilic base produces higher plasma paracetamol concentrations than a hydrophilic base.[46] Information describing the vehicle base as lipophilic was provided in only three studies.[17 20 21]

Parenteral paracetamol

Propacetamol, an injectable prodrug of paracetamol, is completely hydrolysed within 6 min of administration and 1 g of propacetamol yields 0.5 g of paracetamol.[25] Overall, results confirm a clinically relevant analgesic effect with parenteral paracetamol. The quantitative analysis of VAS scores was statistically significant in favour of the parenteral paracetamol groups and consumption of supplementary analgesics was significantly reduced, by 36–50%. Furthermore, in two of the positive studies,[28 32] the use of morphine delivered by patient-controlled analgesia (PCA) may have resulted in the non-significant differences in pain scores between groups. This is consistent with the principle of PCA, in which the patient has the ability to provide satisfactory relief by increasing the cumulative dose of morphine. Finally, in one study, VAS pain scores in the control group were less than 30 mm and the negative findings may have been the result of pain after arthroscopy being a poor model for testing the efficacy of analgesics.[33] Few adverse effects related to parenteral paracetamol were reported.[29 30] However, because of the small number of studies included, no conclusions can be made.

The development of parenteral paracetamol has widened the range of possibilities for a well-tolerated drug being used in the postoperative period, when oral administration is prohibited. Propacetamol is marketed in several European countries.

Route of administration

We identified two studies in which a direct comparison was made between different routes of administration of the same dose of paracetamol in postoperative pain.[30 34] Obviously, more studies are needed to test the evidence for any difference in analgesic efficacy of paracetamol given by different routes. Until such data are available, the route of administration in the postsurgical setting should probably depend on factors such as the presence or absence of gastrointestinal paralysis, nausea and vomiting and sedation.

Combinations of paracetamol and an NSAID

In clinical practice, paracetamol and an NSAID are often given in combination for acute postoperative pain. Concomitant administration of two analgesics with presumably different mechanisms of action may result in an additive analgesic effect. Data support the clinical practice of adding an NSAID to paracetamol to improve postoperative pain. On the other hand, no evidence was found for an improved analgesic effect by adding paracetamol to NSAIDs. The negative results may be related to the limited number of trials available; furthermore, adequate sensitivity was not guaranteed in two of the negative studies as VAS pain scores were less than 30 mm in the control groups.[21 33] No adverse effects attributed to the combination of paracetamol and NSAIDs were reported. However, because of the small number of studies included, the data are insufficient to yield meaningful conclusions.

The conclusions from this systematic review may be considered to be rather tenuous because of the limited eligible data. There is therefore an urgent need for more well-designed large-scale studies, especially on the analgesic efficacy of repeated large rectal doses of paracetamol and on the combination of paracetamol and an NSAID. However, on the basis of the evidence available, we consider paracetamol given by any route to be an important basic analgesic drug in acute postoperative pain management.

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Ketorolac, diclofenac, and ketoprofen are equally safe for pain relief after major surgery[†]

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Background. Ketorolac is approved for the relief of postoperative pain but concerns have been raised over a possible risk of serious adverse effects and death. Two regulatory reviews in Europe on the safety of ketorolac found the data were inconclusive and lacked comparison with other non-steroidal anti-inflammatory drugs The aim of this study was to compare the risk of serious adverse effects with ketorolac *vs* diclofenac or ketoprofen in adult patients after elective major surgery.

Methods. This prospective, randomized multicentre trial evaluated the risks of death, increased surgical site bleeding, gastrointestinal bleeding, acute renal failure, and allergic reactions, with ketorolac *vs* diclofenac or ketoprofen administered according to their approved parenteral and oral dose and duration of treatment. Patients were followed for 30 days after surgery.

Results. A total of 11 245 patients completed the trial at 49 European hospitals. Of these, 5634 patients received ketorolac and 5611 patients received one of the comparators. 155 patients (1.38%) had a serious adverse outcome, with 19 deaths (0.17%), 117 patients with surgical site bleeding (1.04%), 12 patients with allergic reactions (0.12%), 10 patients with acute renal failure (0.09%), and four patients with gastrointestinal bleeding (0.04%). There were no differences between ketorolac and ketoprofen or diclofenac. Postoperative anticoagulants increased the risk of surgical site bleeding equally with ketorolac (odds ratio=2.65, 95% CI=1.51–4.67) and the comparators (odds ratio=3.58, 95% CI=1.93–6.70). Other risk factors for serious adverse outcomes were age, ASA score, and some types of surgery (plastic/ear, nose and throat, gynaecology, and urology).

Conclusion. We conclude that ketorolac is as safe as ketoprofen and diclofenac for the treatment of pain after major surgery.

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Ketorolac tromethamine (trometamol) is an injectable non-steroidal anti-inflammatory drug (NSAID) approved in 1990 for the treatment of postoperative pain. Despite its widespread use during the past decade, concerns have been repeatedly raised over a possible increased risk of serious adverse effects.[1 2] Death, severe haemorrhage, and acute renal failure have been reported following the administration of ketorolac.[3–5] In Europe, the Pharmacovigilance Group of the Committee on Proprietary Medicinal Products (CPMP) has conducted two formal reviews on the safety of ketorolac, but available data were inconclusive and lacked comparison with other NSAIDs approved for use in the postoperative period.[6] The CPMP recommended that a large population study should be carried out to determine the risks of serious adverse effects associated with the use of ketorolac compared with other injectable NSAIDs. We conducted a prospective, randomized multicentre safety trial of ketorolac *vs* diclofenac or ketoprofen administered to adult patients for relief of pain after major surgery. The risks of death, increased surgical site bleeding, gastrointestinal bleeding, acute renal failure, and severe allergic reactions were evaluated.

Patients and methods

Forty-nine hospitals in eight countries in Europe (Belgium, Finland, Ireland, Italy, Portugal, Spain, Switzerland, and UK) provided patients for the trial. The study was conducted in accordance with the Revised Declaration of Helsinki (1996 and 1989). The UK Medicines Control Agency acted as rapporteur to the CPMP, and provided approval for patients to receive anticoagulant drugs while receiving one of the study NSAIDs (which is usually a regulated contraindication in the UK). Informed written consent was obtained from all patients before randomization. Ethics approval was provided by each participating hospital and by the regulatory authorities in each country.

Study population

Adults over 18 yr old, undergoing elective major surgery were entered in the trial. The study procedure defined certain exclusions (patients with known sensitivity to any of the study drugs or other NSAIDs, patients in whom NSAIDs were contraindicated, who were pregnant or lactating, who were to undergo minor, emergency or day-case surgery, or who were ASA physical status class V).

For the purpose of the study, major surgery was defined as a procedure of such complexity as to require admission to hospital for more than 24 h and to require injections of NSAID for relief of postoperative pain. The surgical operation performed was documented and then classified for analysis as *orthopaedic* (e.g. joint replacement, osteotomy, discotomy); *abdominal* (e.g. colectomy, small bowel resection, open cholecystecytomy); *gynaecological* (e.g. total hysterectomy, myometrectomy, oophorectomy); *urological* (e.g. nephrectomy, suprapubic prostatectomy); *plastic/ear, nose and throat (ENT)* (e.g. extensive skin graft, breast reconstruction, rhinoplasty, faciomaxillary procedures); and *others* (including cardiac, vascular, and thoracic surgery). Arthroscopic, laparoscopic, and endoscopic procedures were not included.

Study design

The study was a prospective, randomized multicentre trial of ketorolac *vs* diclofenac or ketoprofen to evaluate the risks of five primary serious adverse outcomes; these were death, increased surgical site bleeding, gastrointestinal bleeding, acute renal failure, and severe allergic reactions. They were defined according to standard diagnostic criteria (Appendix 1). Patients were followed for 30 days after their surgery. Randomization was carried out in blocks at each centre to ensure a balanced allocation between ketorolac and the centre's designated comparator. All patients who were randomized and for whom we had information about outcomes were included in the analysis (intention-to-treat).

Each of the study drugs was administered according to the approved product label for each drug. The maximum daily dose and duration of treatments were: ketorolac, parenteral 90 mg day^{-1} for 2 days followed by oral 40 mg day^{-1} for up to 7 days; diclofenac, parenteral 150 mg day^{-1} for 2 days followed by oral 150 mg day^{-1} for up to 7 days; and ketoprofen, parenteral 200 mg day^{-1} for 2 days followed by oral 200 mg day^{-1} for up to 7 days. If additional analgesia was required, an opioid could be used. Abstracted data were subjected to random audit and tested for inter-observer reliability.

Data analysis

Each of the serious adverse outcomes was analysed by the Mantel–Haenszel test or the Fisher exact test for rare outcomes to test the null hypothesis. Likelihood ratio tests were used to examine heterogeneity of outcomes in different subsets of patients. The Mann–Whitney test was used for continuous variables, and the chi-squared test, or Fisher exact test was used for categorical variables. The only stratification used was by study centre. Risk was assessed by multiple stepwise logistic regressions. Data management was performed by Quintiles Scotland Ltd, and the statistical analysis was performed at the London School of Hygiene and Tropical Medicine. The Steering group of principal investigators was responsible for the design, conduct, and interpretation of this study and was blinded until the final analysis was completed. The Study Safety Committee was un-blinded and provided regular status reports to the UK Medicines Control Agency.

Sample size

An estimate of the required sample size was made using data from a retrospective post-marketing surveillance study which reported a rate of 3.6% for a composite outcome (patients who had died, had increased surgical bleeding, or had gastrointestinal bleeding) in a cohort of patients who received ketorolac and opioid.[7] Using this rate, a sample of 16 000 was calculated to provide over 90% power to detect a relative risk of 1.3 for this composite outcome. Interim power calculations were planned after recruitment of 10, 30, and 60% to determine when a power of at least 80% was achieved to detect a relative risk of 1.5 for the composite outcome. The power calculation was based on a one-sided test using the normal approximation to the Poisson with a 0.025 level of significance, equal to 0.05 on a two-sided test. The significance levels for stopping rules that were established *a priori* by the Safety Committee for death was $P<0.01$ with a relative risk of 3.0, and for serious adverse outcomes was $P<0.001$ with a relative risk of 3.0 separately for increased surgical site bleeding, gastrointestinal bleeding, acute renal failure, and severe allergic reactions. The Safety Committee recommended to stop the study after reviewing the data on the estimated 60% of patients. The time to obtain agreement from the CPMP, and the 30-day observation period resulted in additional patients being entered in the study before the database was closed. A total of 11 302 patients were randomized. This sample provided over 80% power to detect a relative risk of 1.5 at the rate of 1.24%, which was found for the composite outcome.

Results

Fifty-seven of the 11 302 randomized patients were lost to follow-up, leaving 11 245 patients who completed the trial and were entered in the database for the outcome analysis. Of these, 5634 patients received ketorolac, and 5611 patients received one of the comparator NSAIDs. Procedure violations occurred in 33 patients (0.3%) who met an exclusion criterion but were entered into the study. The median number of days in hospital (interquartile range (IQR)) was 6 (4–9) and was no different between ketorolac and the comparators. Ninety-seven per cent of patients received parenteral injections of the assigned study drug, 53% received oral doses of the same drug during the hospital stay, and 32% received oral doses after discharge. The doses of study medication that were administered varied by country. For example, the median (IQR) dose for parenteral ketorolac varied from 40 (40–70) to 100 (70–160) mg; for diclofenac from 75 (75–150) to 150 (75–225) mg, and for ketoprofen from 200 (100–250) to 400 (300–400) mg. In patients who had serious adverse outcomes, the median number of days of parenteral injections was 1 for all three study drugs, and the median number of days of oral administration was 4. The median maximum daily parenteral dose in patients with serious adverse outcomes was 30, 150, and 100 mg for ketorolac, diclofenac, and ketoprofen, respectively. Doses of parenteral study drug in excess of the approved level were administered in only 1.1% of patients who received ketorolac, in 2.2% of patients who received diclofenac, and in 0.7% of patients who received ketoprofen. A chi-squared test for trend between dose categories and the composite outcome was not significant for any of the study drugs. The baseline characteristics of patients were similar in each study drug group (Table 1) There were 766 patients classified as ASA III or IV, and 3208 patients over the age of 60 yr.

Table 1 Baseline characteristics of 11 302 randomized patients for ketorolac and comparator NSAIDs. Fifty-four patients were lost to follow-up leaving 11 245 patients entered in the database

Factor	**Ketorolac *vs* comparator** *n*=5658, *n*=5644	**Ketorolac *vs* diclofenac** *n*=2585, *n*=2582	**Ketorolac *vs* ketoprofen** *n*=3073, *n*=3062
Age mean (SD) [range]	49 (17), 49 (16) [19–94]	48 (17), 47 (17) [19–90]	49 (16), 50 (16) [19–94]
Females (%)	3429 (61), 3382 (60)	1456 (56), 1467 (57)	1973 (64.1), 1915 (63)
ASA I	3505 (62), 3505 (62)	1602 (62), 1589 (62)	1903 (62), 1916 (63)
ASA II	1769 (31), 1750 (31)	760 (29), 771 (30)	1009 (33), 979 (32)
ASA III	364 (6), 373 (7)	210 (8), 211 (8)	154 (5), 162 (5)
ASA IV	15 (<1), 14 (<1)	13 (<1), 11 (<1)	2 (<1), 3 (<1)
Type of surgery			
Orthopaedic	1670 (30), 1687 (30)	446 (17), 458 (18)	1224 (40), 1229 (40)
Abdominal	724 (13), 774 (14)	208 (8), 210 (8)	516 (17), 564 (18)
Plastic/ENT	844 (15), 784 (14)	612 (24), 576 (22)	232 (8), 208 (7)
Gynaecology	1067 (19), 1055 (19)	519 (20), 540 (21)	548 (18), 515 (17)
Urology	335 (6), 333 (6)	299 (12), 293 (11)	36 (1), 40 (1)
Other	1026 (18), 1028 (12)	508 (20), 517 (20)	518 (17), 511 (17)

Table 2 Number (%) of patients with outcomes (A) ketorolac *vs* comparator in 11 245 patients; (B) ketorolac *vs* ketoprofen in 6101 patients, (C) ketorolac *vs* diclofenac in 5144 patients *Calculated using the Fisher exact test

Outcome			Odds ratio (95% CI)	*P*-value
(A)	Ketorolac *n*=5634	Comparator *n*=5611		
Death	9 (0.2)	10 (0.2)	0.90 (0.37–2.19)	0.82*
Surgical site bleed	61 (1.1)	56 (1.0)	1.07 (0.75–1.54)	0.66
Gastrointestinal bleed	0 (0)	4 (0.1)	0 (0–0.96)	0.06*
Acute renal failure	3 (0.1)	7 (0.1)	0.42 (0.11–1.62)	0.23*
Allergic reaction	5 (0.1)	7 (0.1)	0.70 (0.22–2.17)	0.58*
Composite outcome	70 (1.2)	69 (1.2)	(0.72–1.39)	0.95
Any outcome	77 (1.4)	78 (1.4)	0.97 (0.71–1.33)	0.92
Other adverse reports	123 (2.2)	131 (2.3)	0.94 (0.73–1.19)	0.59
No outcome	5557 (98.6)	5533 (98.6)	1.0 (1.0–1.01)	0.92
(B)	Ketorolac *n*=3058	Ketoprofen *n*=3043		
Death	0 (0)	5 (0.2)	0 (0–0.76)	0.03*
Surgical site bleed	22 (0.7)	19 (0.6)	1.13 (0.62–2.08)	0.65
Gastrointestinal bleed	0 (0)	3 (0.1)	0 (0–1.27)	0.12*
Acute renal failure	1 (<0.1)	3 (0.1)	0.32 (0.03–3.07)	0.37*
Allergic reaction	2 (0.1)	4 (0.1)	0.48 (0.09–2.55)	0.45*
Composite outcome	22 (0.7)	26 (0.9)	0.83 (0.47–1.45)	0.55
Any outcome	25 (0.8)	30 (1.0)	0.81 (0.48–1.37)	0.49
Other adverse reports	48 (1.6)	49 (1.6)	0.98 (0.66–1.45)	0.90
No outcome	3033 (99.2)	3013 (99.0)	1.0 (1.0–1.01)	0.49
(C)	Ketorolac *n*=2576	Diclofenac *n*=2568		
Death	9 (0.3)	5 (0.2)	1.81 (0.61–5.39)	0.42*
Surgical site bleed	39 (1.5)	37 (1.4)	1.05 (0.67–1.63)	0.83
Gastrointestinal bleed	0 (0)	1 (<0.1)	0 (0–1.90)	0.50*
Acute renal failure	2 (0.1)	4 (0.2)	0.50 (0.09–2.69)	0.45*
Allergic reaction	3 (0.1)	3 (0.1)	(0.20–4.91)	1.00*
Composite outcome	48 (1.9)	43 (1.7)	1.11 (0.74–1.66)	0.61
Any outcome	52 (2.0)	48 (1.9)	1.08 (0.73–1.58)	0.70
Other adverse reports	75 (2.9)	82 (3.2)	0.91 (0.67–1.24)	0.56
No outcome	2524 (98.0)	2520 (98.1)	1.0 (0.99–1.01)	0.70

The number and per cent of patients with serious adverse outcomes are summarized in Table 2A for ketorolac *vs* comparator, Table 2B for ketorolac *vs* ketoprofen and Table 2C for ketorolac *vs* diclofenac. There were 155 patients (1.4%) with at least one serious adverse outcome but no difference was found for any outcome between ketorolac and the comparators.

There were 19 deaths (0.17%); the causes of death were cardiac arrest (10 patients), sepsis (three patients), pulmonary embolism (two patients), intraoperative haemorrhage (one patient), renal failure secondary to peritonitis (one patient), metastatic carcinoma (one patient), and respiratory failure (one patient). None were considered to be related to the use of a study drug. Twelve patients had a severe allergic reaction (0.11%), 10 patients had acute renal failure (0.09%), and four patients had gastrointestinal bleeding (0.04%).

The most frequent outcome was increased surgical site bleeding in 117 patients (1.04%) of whom 61 received ketorolac, and 56 received one of the comparators. The risk of surgical site bleeding was 3.05 times higher with the use of postoperative anticoagulants. Forty-one per cent of patients received an anticoagulant after surgery including fractionated low-molecular-weight heparin (LMWH) in 2929 patients (26%), and low-dose unfractionated heparin (UFH) in 1552 patients (13.8%). The risk of surgical site bleeding was generally higher with low-dose UFH than with fractionated LMWH. More patients received anticoagulants after orthopaedic (55%), gynaecology (55%), abdominal (47%), and urology (34%) surgery than after plastic/ENT surgery (14%). Patients who received ketorolac (odds ratio=2.65, 95% CI=1.51–4.67) or comparator NSAID (odds ratio=3.58, 95% CI=1.93–6.70) were equally likely to experience a higher risk of surgical site bleeding when an anticoagulant was administered (Table 3).

Other risk factors for serious adverse outcomes were age, ASA score, history of regular alcohol use, plastic/ENT surgery, gynaecological surgery, and urological surgery (Table 4). However, none of these risks were any different between ketorolac and diclofenac or ketoprofen.

Standard reporting of all adverse events using the WHOART terminology was done in our study. There were 254 patients (2.3%) with these adverse events of which 123 patients received ketorolac and 131 patients received one of the comparators (Table 2A–C).

Discussion

This study was designed to answer the concerns of the CPMP of a possible increased risk of serious adverse outcomes with ketorolac compared with other NSAIDs. The addition of a placebo group or other treatment group, such as an opioid, was not considered relevant as there was no concern over safety in patients not receiving an NSAID. Of

Table 3 Risk of postoperative surgical site bleeding with ketorolac and comparator with and without anticoagulant POB=postoperative surgical site bleeding

	Ketorolac *n* (%) with POB	Total	Comparator *n* (%) with POB*	Total	Odds ratio (95% CI) ketorolac *vs* comparator	*P*-value
Any anticoagulant	39 (1.7)	2283	39 (1.7)	2235	0.98 (0.61–1.57)	0.98
No anticoagulant	21 (0.6)	3256	16 (0.5)	3281	1.32 (0.66–2.66)	0.50
Anticoagulant *vs* no anticoagulant	2.65 (1.51–4.67)		3.58 (1.93–6.70)			
Odds ratio (95% CI)	*P*<0.001		*P*<0.001			

Table 4 Risk factors for the composite outcome (death, surgical site bleed, or gastrointestinal bleed) *Odds ratio is for 10-yr increase †Odds ratio is for one unit increase

Factor	Odds ratio (95% CI)	*P*-value
Age*	1.18 (1.04–1.34)	0.012
ASA score†	1.48 (1.10–1.98)	0.009
History of regular alcohol use	1.50 (1.04–2.17)	0.031
Postoperative anticoagulant	2.52 (1.69–3.76)	<0.001
Surgery: plastic/ENT	3.45 (2.02–5.89)	<0.001
Surgery: gynaecology	2.65 (1.72–4.10)	<0.001
Surgery: urology	2.46 (1.28–4.71)	0.007

particular interest was any increased risk in elderly patients and in those with serious systemic disease who had undergone major surgery. We found the risk of serious adverse outcomes was very low in this study and did not identify any difference between ketorolac and diclofenac or ketoprofen for any outcome.

Gastrointestinal effects

Gastrointestinal perforations, ulceration, and bleeding (PUBs) have been reported with all NSAIDs after chronic use.[8 9] However, the risk of serious gastrointestinal adverse effects with NSAIDs, including ketorolac, is very low after short-term perioperative use[10]. A review of 15 postoperative placebo-controlled trials reported only one case of serious gastrointestinal bleeding in 1520 patients, of whom 927 had received an NSAID.[10] Several studies have reported an increased risk of serious gastrointestinal bleeding in patients over 60 yr old, in women, in patients with a history of peptic ulceration, in smokers, and in patients who consume excessive amounts of alcohol.[11–13] A retrospective post-marketing surveillance study in over 20 000 patients who received ketorolac or opioid,[7] reported a small increased risk of gastrointestinal bleeding with ketorolac (odds ratio=1.30, 95% CI=1.11–1.52) but no significant increased risk of surgical bleeding (odds ratio=1.02, 95% CI=0.95–1.10). These risks were significantly increased further in patients over 70 yr, and in patients who received excessive doses of ketorolac for more than 5 days. In our study, there were only four patients (0.04%) who had gastrointestinal bleeding. None of these patients received ketorolac.

Postoperative surgical site bleeding

The use of NSAIDs after surgery may increase the risk of bleeding by their antiplatelet effects;[2] however, the evidence of increased bleeding is conflicting. Some studies have reported no increased bleeding with ketorolac,[1] or diclofenac[14] when administered after transurethral prostatectomy, a procedure that is commonly associated with postoperative bleeding. In contrast, aspirin or other NSAIDs taken preoperatively increased the risk of postoperative bleeding after prostatectomy.[15] Bleeding time is increased with NSAID therapy and for ketorolac this increase is 312–468 s[16] (normal ~600 s). However, the antiplatelet effects of NSAIDs do not appear to significantly alter postoperative coagulation and may be protective for myocardial infarct and thromboembolism.[17]

In our study, the risk of postoperative surgical site bleeding was increased when anticoagulant drugs were used for thromboprophylaxis after surgery, but was no different between ketorolac and the two other NSAIDs. Low-dose UFH was associated with a higher risk of bleeding (2.5%) than fractionated LMWH preparations (1.3%). A recent meta-analysis of randomized trials in general surgery has reported that low-dose LMWH was safer than low-dose UFH, but at higher doses there was an increased risk of major haemorrhage with both preparations.[18] A possible interaction between NSAID and anticoagulant drugs cannot be ruled out, but this does not appear to involve a clinically important increase in bleeding time.[19] Some types of surgery in our study were associated with a higher risk of surgical site bleeding, independent of the use of post-operative anticoagulants. Plastic/ENT surgery increased the risk of surgical site bleeding by 3.5 times, gynaecological surgery increased the risk by 2.7 times, and urological surgery increased the risk by 2.5 times. A recent study in 215 patients after breast reconstruction found no increased incidence of haematoma with ketorolac,[20] and in our study we found no difference for increased surgical site bleeding between ketorolac and the two comparators in patients who had undergone plastic/ENT surgery or other types of surgery. Whereas the absolute risk of increased surgical site bleeding appears to be small, further studies are needed to evaluate the potential interaction and increased risk with concomitant NSAID and anticoagulant use in specific types of surgery.

Renal effects

Cyclo-oxygenase-1 and -2 are important components of the control of glomerular filtration and excretion of urine.[21] NSAIDs can interfere with renal function through the inhibition of both forms of cyclo-oxygenase. There are four toxic effects of NSAIDs on the kidney: acute ischaemic renal insufficiency, acute interstitial nephritis, analgesic-associated nephropathy, and progressive hypertensive nephropathy. Reports of acute renal failure after ketorolac and other NSAIDs are mainly the result of acute ischaemic effects.[22] Other factors that increase the risk of acute renal failure include hypovolaemia, cardiac failure, ascites, and liver cirrhosis.[21] A large retrospective cohort found no significant association with ketorolac in patients who developed postoperative acute renal failure.[23] A meta-analysis of eight randomized trials of NSAID effects on postoperative renal function reported only a minor transient decrease in creatinine clearance after ketorolac, diclofenac, indomethacin, or ibuprofen.[24] Ten patients (0.1%) had acute renal failure in our study, three cases were reported after ketorolac and seven cases after the comparator NSAIDs. There was no significantly increased risk of acute renal failure in 42 patients with a history of renal insufficiency, or 72 patients with a history of congestive heart failure.

Allergic reactions

Allergic reactions to NSAIDs are uncommon and include skin rash, bronchospasm, and anaphylaxis. It has been estimated that between 5 and 10% of asthmatics are sensitive to aspirin and acidic NSAIDs.[25] Ketorolac has been reported to cause acute bronchospasm in aspirin-intolerant patients.[26] Systemic anaphylaxis associated with NSAID is very rare but is often fatal. There were 12 patients who experienced severe allergic reactions in our study. None of these patients died and no difference was found between ketorolac and the comparator NSAIDs.

The overall risk of serious adverse effects with ketorolac and the comparator NSAIDs was very low in this study. We found no evidence that the risk of serious adverse effects with ketorolac was any different to that with ketoprofen or diclofenac. It should be noted that these drugs were administered according to their approved dose and duration of treatment. We conclude that parenteral and oral ketorolac, ketoprofen, and diclofenac are equally safe for the treatment of pain after major surgery when administered according to the approved product label.

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Appendix 1

Criteria for serious adverse outcomes

Death

Patients who were randomized and entered into the trial and who died from any cause during the 30 days after surgery. The cause of death and all related medical information was documented.

Increased surgical site bleeding

An overt or covert loss of blood from the operative site that requires medical intervention and/or is excessive and/or is unexpected. For internal bleeding, evidence of shock, hypotension (<100 mm Hg systolic, <60 mm Hg diastolic), decreased haemoglobin and haematocrit, and/or increased blood urea and creatinine. For external bleeding, evidence of excessive bleeding into surgical drains and/or wound dressings, shock, hypotension, hypovolaemia, decreased haemoglobin and haematocrit, and/or increased blood urea and creatinine.

Gastrointestinal bleeding

An overt loss of blood from the gastrointestinal tract (haematemesis and/or melaena and/or blood per rectum) that requires medical intervention including endoscopy, transfusion of blood and/or i.v. fluids, or surgical reoperation to control bleeding, with evidence of shock, hypotension, decreased haemoglobin and haematocrit, and/or increased blood urea and creatinine.

Acute renal failure

Renal impairment that results in 100% increase in serum creatinine and/or oliguria, and/or dialysis, with evidence of increased blood urea and increased potassium, i.v. pyelogram, renal biopsy, x-rays, and/or ultrasound.

Severe allergic reaction

An allergic reaction that requires inhaled and/or i.v. medication, and/or intubation, and/or ventilation, with evidence of bronchspasm, dyspnoea, apnoea, angioedema, laryngeal oedema, shock, hypotension, anaphylaxis, skin rash, inotropic drugs, adrenergic drugs, antihistamines, and/or i.v. corticosteroids.

Appendix 2

The Investigators

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Comparison of predictive models for postoperative nausea and vomiting

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Background. In order to identify patients who would benefit from prophylactic amtiemetics, six predictive models have been described for the risk assessment of postoperative nausea and vomiting (PONV). This study compared the validity and practicability of these models in patients undergoing general anaesthesia.

Methods. Data were analysed from 1566 patients who underwent balanced anaesthesia without prophylactic antiemetic treatment for various types of surgery. A systematic literature search identified six predictive models for PONV. These models were compared with respect to validity (discriminating power and calibration characteristics) and practicability. Discriminating power was measured by the area under the receiver operating characteristic curve (AUC) and calibration was assessed by weighted linear regression analysis between predicted and actual incidences of PONV. Practicability was assessed according to the number of factors to be considered for the model (the fewer factors the better), and whether the score could be used in combination with a previously applied cost-effective concept.

Results. The incidence of PONV was 600/1566 (38.1%). The discriminating power (AUC) obtained by the models (named according to the first author) using the risk classes from the recommended prophylactic concept were as follows: Apfel, 0.68; Koivuranta, 0.66; Sinclair, 0.66; Palazzo, 0.63; Gan, 0.61; Scholz, 0.61. For four models, the following calibration curves (expressed as the slope and the offset) were plotted: Apfel, y=0.82x+0.01, r^2=0.995; Koivuranta, y=1.13x–0.10, r^2=0.999; Sinclair, y=0.49x+0.29, r^2=0.789; Palazzo, y=0.30x+0.30, r^2=0.763. The numbers of parameters to be considered were as follows: Apfel, 4; Koivuranta, 5; Palazzo, 5; Scholz, 9; Sinclair, 12; Gan, 14.

Conclusion. The simplified risk scores provided better discrimination and calibration properties compared with the more complex risk scores. Therefore, simplified risk scores can be recommended for antiemetic strategies in clinical practice as well as for group comparisons in randomized controlled antiemetic trials.

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Today, the incidence of postoperative nausea and vomiting (PONV) still appears to be about 30%.[1–3] Despite this, the benefit of routine prophylactic antiemetic treatment has been questioned because antiemetics may have side-effects[4] and therefore patient satisfaction may not necessarily improve.[5] The number of patients needed to be treated (NNT) to prevent one patient from suffering PONV is at best in the range of five when the event rate is relatively high,[6] so that unnecessary costs may arise if patients are receiving prophylactic compared with therapeutic antiemetic treatment. However, totally neglecting the potential of prophylactic antiemetics is by no means acceptable: PONV may lead to severe medical complications with sudden airway compromise,[7] for example. The cost of prophylactic treatment may be contained by keeping the number of patients needed to be treated small through

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the use of a multimodal approach for identifying patients at high risk.[8] Patient satisfaction may well improve if patients with a high risk of PONV are treated.[5] In contrast, not using prophylactic treatment in these patients may result in considerable costs, far exceeding the costs of prophylactic antiemetic treatment.[9]

In order to identify patients at high risk who would benefit from a cost-effective antiemetic treatment,[10 11] several models and scores have been proposed. As one of the risk scores predicting the probability of PONV has been developed by our centre, we decided to compare its validity and practicability with all other published models in patients from a different centre.

Patients and methods

The study was approved by the local ethics committee and informed consent was obtained from every patient.

All patients received balanced anaesthesia with isoflurane, enflurane, sevoflurane or desflurane in nitrous oxide/oxygen (ratio 2:1). Propofol, thiopental or etomidate was used for induction at clinically required doses. None of the patients included in the study received perioperatively (at least 24 h before and after anaesthesia) any drug with potential antiemetic properties. Vecuronium, atracurium or mivacurium was used to facilitate intubation and repeat doses were only given if needed, so that the need for antagonizing neuromuscular blockade (atropine 0.5 mg and pyridostigmine 0.1 mg kg^{-1}) was rare (approximately 3%). The most frequently used anaesthetic technique (60% of cases) consisted of propofol, fentanyl and vecuronium for induction followed by desflurane in nitrous oxide/oxygen for maintenance and additional doses of fentanyl as required.

Nausea and vomiting were assessed in the postanaesthetic care unit by specially instructed nurses or anaesthesiologists. Vomiting or retching was considered as an emetic episode. Nausea was assessed on a four-point verbal rating scale (none, mild, moderate, severe) and patients were interviewed explicitly before transfer to the ward. During the afternoon of the same day (at least 6 h postoperatively) and during the following day (at least 24 h postoperatively), further standardized postoperative visits were performed. A patient was considered to have had PONV if any degree of nausea and/or any emetic episodes occurred in at least one of the periods investigated.

A systematic search of a literature database (http://www.nlm.nih.gov/databases/freemedl.html) revealed 11 studies dealing with risk models and PONV[1 2 12–19] when the following search terms were used: 'postoperative' together with (=logical AND) 'score' AND ('nausea' OR 'vomiting') AND 'risk'. However, we excluded five studies because they did not present a predictive model or were validations of previous scores[1 13 16 18 19] and two further studies from our centre because they dealt only with postoperative vomiting and not with PONV.[15 16] Thus, four scores for predicting PONV were identified initially.[2 12 14 17] Additional hand searching of abstracts and other sources revealed two additional models,[20 21] so that a total of six models/scores were found for the prediction of PONV.

For each patient, four probabilities of PONV were calculated according to the four scores.[2 12 14 17] The remaining two models allowed classification of patients only into those with low (less than 30%) and high (more than 30%) risk.[20 21] Either probability of PONV or classification into low or high risk was used to create so-called receiver operating characteristic (ROC) curves, as described previously.[2]

In short, a predictive model provides for an individual a probability of an event between 0 and 1. In practice, a decision is needed about whether this event will occur. Depending on the value of the probability that an event is expected to occur (decision criterion), the sensitivity and specificity of a predictive model vary. The ROC curve displays the correlation between the sensitivity and the specificity for all possible decision criteria. Therefore, the area under the ROC curve (AUC) is an overall measure of a risk score/model to discriminate patients with PONV from those without PONV (discriminating power) and is frequently used to compare different risk scores/models.

However, it should be noted that most scores and models have a limited number of outcome variables, resulting in a limited number of possible decision criteria. As ROC curves are constructed by direct lines between the data pairs of specificity and sensitivity, scores/models with fewer risk classes may result in a smaller AUC. Thus, the AUCs of the different scores/models were compared in three ways.

First, the AUC was calculated from the ROC curve that was given by the original scores/models.

Secondly, the four scores that allowed the calculation of the probability of PONV were adapted to the risk classes (<10%, low risk; 10–30%, mild to moderate risk; 30–60%, high risk; >60%, extremely high risk) recommended by White and Watcha.[10 11] This resulted in three risk classes for the scores from Koivuranta and colleagues and Apfel and colleagues and four risk classes for the scores from Palazzo and Evans and from Sinclair and colleagues, so that all scores had a similar number of decision criteria and were directly comparable. Thirdly, ROC curves with their AUC were calculated for the recommendation of Gan or Scholz and colleagues to apply prophylactic antiemetic treatment if three or more points were obtained[20] or if the risk was greater than 30%.[21] The latter also applied to the risk scores with more than one decision criterion,[2 12 14 17] i.e. the information was collapsed to a dichotomous outcome so that a direct comparison of all scores was possible.

Differences between the AUC of $P<0.05$ were considered to be statistically significant.

For the four scores for which the probability of PONV could be determined,[2 12 14 17] the predicted incidences were compared with the real incidences and weighted linear regression analysis was applied across the recommended

Table 1 Patient characteristics with frequencies and odds ratio for PONV. Data are presented as number of patients (%) except age and duration, which are given in years and minutes (25th and 75th percentiles), and the calculated odds ratios using multiple logistic regression analysis for each factor, with the 95% confidence interval. The surgical categories refer to the categories used in some risk models. Some patients fitted more than one classification, whereas 292 patients did not fit any *$P<0.001$, all other P values are >0.1

	n	%	Odds ratio	95% confidence interval
Total	1566	100	–	–
Age (yr), odds ratio per decade	46.1	30–61	0.96	0.90–1.02
Female	699	44.6	2.91*	2.30–3.70
Previous history of PONV	569	36.3	1.71*	1.36–2.15
Previous history of motion sickness	134	8.6	1.73*	1.17–2.57
Previous history of PONV or motion sickness	634	40.5	1.83*	1.46–2.29
Obesity (body mass index >30)	214	13.7	0.82	0.59–1.13
Anxiety (assessed preoperatively)	336	21.5	1.25	0.95–1.63
Non-smoking status	1098	70.1	1.83*	1.41–2.37
Duration of anaesthesia (min), odds ratio (per h)	123	84–165	1.36*	1.22–1.51
Gynaecological operations, all (no curettages)	52	3.3	1.11	0.57–2.20
Gynaecological laparoscopies	47	3	1.63	0.86–3.09
Orthopaedic procedures, shoulder	146	9.3	1.37	0.93–2.02
Orthopaedic procedures, knee	201	12.8	1.10	0.77–1.55
Orthopaedic procedures, others	538	34.4	0.93	0.72–1.21
Ophthalmic operations, no strabismus surgery	75	4.8	1.36	0.78–2.37
ENT operations, all	93	5.9	1.00	0.62–1.63
ENT operations, middle ear operations	21	1.3	1.56	0.61–4.00
Abdominal surgery, all (including all laparoscopies)	217	13.9	1.23	0.83–1.83
Laparoscopic cholecystectomies	42	2.7	2.85*	1.40–5.81
Use of intraoperative opioids	1559	99.6	1.86	0.32–10.78
Use of postoperative opioids	1078	68.8	1.32	1.01–1.73
Use of perioperative opioids	1563	99.8	1.85	0.15–22.45
Patients with PONV	600	38.3	N/A	N/A

classes. This regression analysis resulted in calibration curves for which a slope of 1.00 or 45° with no offset would represent a perfect fit. A deviation from the slope of less than 25% was defined to be clinically acceptable.

The risk calculations were performed using Excel 2000 (Microsoft, USA). Logistic regression analysis was performed with SPSS 9.0 (SPSS, Chicago, IL, USA). The area under the ROC curve was calculated using MedCalc 4.2 (Mariakerke, Belgium).

Results

An average of 38.3% (600/1566) patients suffered from PONV (Table 1). The population analysed represented 885 orthopaedic, 75 ophthalmic, 93 ENT, 170 gastrointestinal abdominal and 52 gynaecological surgical procedures and 292 procedures of other types. Of the 885 orthopaedic patients, 146 had shoulder, 201 knee, 89 hip and 449 other types of orthopaedic procedures. However, Table 1 does not display all numbers for all types of procedure. The selection was based on the types that were considered in at least one of the risk models. For example, one score[17] considered an odds ratio of 5.91 for shoulder, 2.82 for knee and 2.57 for all other orthopaedic surgery. The odds ratio in this population, however, revealed no significant effect of orthopaedic surgery on PONV (Table 1). Another score defined surgery involving the abdominal cavity as a risk factor for PONV.[21] This included all laparoscopic surgery, so that 170 gastrointestinal procedures [laparotomies and laparoscopies (42)] plus 47 gynaecological laparoscopies resulted in 217 procedures involving the abdominal cavity. Again, as in all other types of surgeries investigated here, procedures involving the abdominal cavity had no significant effect on PONV (Table 1).

The discriminating power of the original scores from Apfel, Koivuranta and Sinclair and their colleagues was significantly higher than that of the scores from Palazzo and colleagues, Gan, and Scholz and colleagues (Table 2; all $P<0.05$). The application of the four scores to the classes recommended by White and Watcha did not lead to a significant decrease in the AUC ($P>0.05$). When the classification was made according to low-risk patients (less than 30%), in whom no prophylaxis should be given, or high-risk patients, in whom prophylactic antiemetic strategies should be considered (more than 30%), all predictions of the scores which enabled calculation of the probability decreased significantly ($P<0.05$).

No calibration curve was possible with the models that simply classified patients into two risk groups without giving an expected incidence.[20] [21] The scores from Apfel and Koivuranta and their colleagues showed a good correlation between the predicted and actual incidences of PONV (Fig. 1A and B). This was not the case for the scores from Palazzo and Sinclair and their colleagues, for which the incidence of patients classified as having a low risk (<10%) was above 20% (Fig. 1C and D).

Table 2 Area under the ROC curve (AUC) for the six risk scores Three applications were defined according to (A) the original description of the authors, (B) the four categories suggested by Watcha *et al.* and (C) a binary decision with a limit of 30% CI=confidence interval; N/A=not applicable

Authors	**(A) Original model**		**(B) Watcha model**		**(C) Binary model**	
	AUC	**95% CI**	**AUC**	**95% CI**	**AUC**	**95% CI**
Apfel *et al.*[2]	0.68	0.66–0.71	0.68	0.65–0.70	0.64	0.62–0.66
Gan[20]	0.61	0.58–0.63	N/A	–	0.61	0.58–0.63
Koivuranta *et al.*[14]	0.70	0.67–0.72	0.66	0.64–0.69	0.60	0.58–0.63
Palazzo and Evans[12]	0.64	0.62–0.67	0.63	0.60–0.65	0.62	0.59–0.64
Scholz *et al.*[21]	0.61	0.58–0.63	N/A	–	0.61	0.58–0.63
Sinclair *et al.*[17]	0.68	0.66–0.71	0.66	0.64–0.69	0.61	0.59–0.63

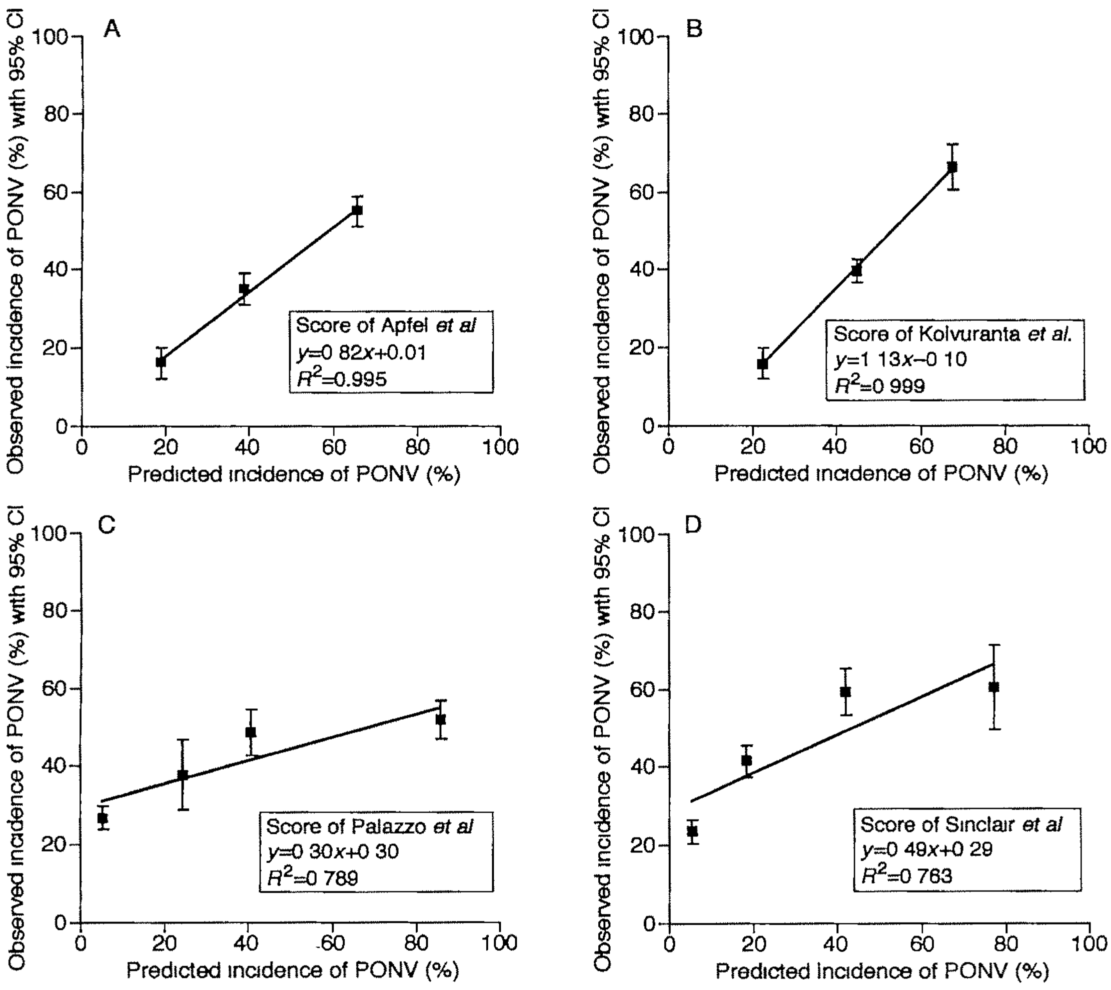

Fig 1 Calibration curves, i.e correlations between predicted (x) and actual (y) incidences, for the scores adapted to the risk classes suggested by White and Watcha to allow direct comparisons.[10] [11] (A) Score of Apfel *et al*[2] (B) Score of Koivuranta *et al*[14] (C) Score of Palazzo *et al*[12] (D) Score of Sinclair *et al.*[17] The calibration curves are weighted according to the number of patients per group.

Discussion

A comparison of all currently available models for predicting the probability of PONV in patients undergoing balanced anaesthesia revealed significant differences concerning their validity and practicability. Among these models, the simplified scores from Apfel and Koivuranta and their colleagues[2] [14] appeared to be suitable tools for clinicians to put the rational and cost-effective antiemetic concept into practice[10] and for researchers to perform group comparisons in randomized controlled trials.[11] [22]

Palazzo and Evans were the first to apply logistic regression analysis to patients undergoing minor orthopaedic surgery under well-defined conditions.[12] Although they did not originally intend to develop a score with universal applicability for predicting PONV, the first

Table 3 Comparison of the six scores Note that the simplified models by Apfel *et al.*[2] and Koivuranta *et al*[14] have the best discrimination and calibration despite considering just four or five risk factors. AUC=area under the receiver operating characteristic curve

	Apfel *et al.*[2]	**Gan[20]**	**Koivuranta *et al.*[14]**	**Palazzo and Evans[12]**	**Scholz *et al.*[21]**	**Sinclair *et al.*[17]**
Discriminating properties >0.65 (AUC)	+ (0.68)	– (0.61)	+ (0.70)	– (0.64)	– (0.61)	+ (0.68)
Risk can be calculated as percentage (yes/no)	+ (yes)	– (no)	+ (yes)	+ (yes)	– (no)	+ (yes)
Risk calculated in percent with acceptable calibration (yes/no, slope and offset)	+ (yes) (0.82 and 0.01)	– (N/A)	+ (yes) (1.13 and –0.10)	– (no) (0.30 and 0.30)	– (N/A)	– (no) (0.49 and 0.29)
Applicable to Watcha's recommendations	+ (yes)	– (no)	+ (yes)	+ (yes)	– (no)	+ (yes)
Ease of use I (simplified model possible)	+ (yes)	+ (yes)	+ (yes)	– (no)	+ (yes)	– (no)
Ease of use II (number of predictors needed)	+ (4)	– (14)	+ (5)	+ (5)	– (9)	– (12)

validation with 400 patients suggested that their model could well be transferred to other types of surgery.[13] However, in this validation, the calibration curve presented a flattened slope of 0.3 and an offset of 30%. Thus, patients who were classified as having a low risk showed a much higher incidence, while patients who were really at low risk were not identified. The reason for this difficulty may lie in the extremely high odds ratio of 53.0 for a positive history of PONV in the data from Palazzo and Evans, because of the smaller study population,[12] while the odds ratio of this risk factor was between 2.27 and 3.13 in all other studies[1,2,13,14,17] and 1.71 in this population (Table 1). Although this calibration makes this score less suitable for clinical practice, we would like to point out that this model for the prediction of PONV has stimulated several other investigators to apply this method on a larger scale.

The score from Koivuranta and colleagues appeared to be one of the best models in the population investigated.[14] First, they identified all significant factors and calculated the corresponding AUC. Interestingly, the type of operation did not have any significant effect on PONV in their original multivariable model, i.e. when corrections for the other predictors were considered. Secondly, they reduced the number of predictors from eight to five and found no effect on overall discriminating power. Thirdly, they observed that the coefficients of the predictors were all quite similar. Thus, they investigated whether a model which was based only on the simple number of risk factors resulted in a similar AUC compared with the rather complicated logit model, which considers different coefficients for each factor. They found that such a score can be simplified without a significant decrease in the AUC. In our view, simplification is an important characteristic for a score suitable for daily practice (Table 3).

The calibration curve of the model of Sinclair and colleagues appeared to have an offset of about 30%, which is corroborated by a recent study that revealed a similar offset of 27%.[23] Therefore, like the score of Palazzo and Evans, patients classified as low-risk (<10%) showed a much higher incidence (25%), while true low-risk patients were not appropriately identified. Ascribing this discrepancy to the fact that the score of Sinclair and colleagues was developed for ambulatory surgical patients conflicts with the expectation that, under comparable conditions (same procedures, same anaesthetic techniques, etc.), PONV should occur more frequently in outpatients than in inpatients, as motion sickness may be a contributing factor. In contrast, the incidence reported by Sinclair and colleagues was only 9.1%, which is far below the known average incidence of 20–40% from all other prospective studies on PONV.[1,2,12,14] Under-reporting of PONV was suggested as a possible problem in the study of Sinclair and colleagues.[17] Another difficulty with this model is the flattened slope of only 0.5 (~30°). Comparison of the odds ratio of our population with those described by Sinclair and colleagues revealed that, in accordance with other multivariable analyses,[1,13,14] most types of surgery did not affect PONV significantly, while odds ratios from Sinclair and colleagues ranged between 2.57 (orthopaedic surgery) and 6.68 (plastic surgery). If these odds ratios do not apply to other centres, such as the population investigated here, this could result in a flatter calibration curve, as the score would lead to some patients being estimated to have a much higher or lower risk (depending on the type of surgery) while the real incidence would not have been affected to that extent. In addition, the risk can only be estimated using a rather complicated formula, making the use of this score less practical under clinical conditions (Table 3).

The score of Apfel and colleagues[2] is a result of collaboration between a German and a Finnish centre. Reanalysing their previously published data,[14–16] the authors investigated whether risk scores were valid for different centres and whether risk scores based on logistic regression coefficients could be simplified without loss of discriminating power. While testing different scores, they developed a final score from a joint data set which consisted of four predictors: female gender, history of motion sickness or PONV, non-smoking status and the use of postoperative opioids. If none, one, two, three or four of these risk factors were present, the incidences of PONV were 10, 21, 39, 61 and 79% respectively. Owing to the definition of a 'low risk' as less than 10%, patients with no risk factor or one risk factor were classified into the mild to moderate risk class. However, for practical purposes it may make more sense to classify patients with no risk factors as low-risk patients. We believe that this will be even more reasonable when the recommendation of White and Watcha is applied.[10 11] In the population studied here, the score of Apfel and colleagues gave an acceptable AUC of 0.68 and a slope very close to 1. Similar positive results in favour of the score of Apfel and colleagues[2] have now been obtained by Pierre and colleagues.[23] In the light of this, and its easy applicability, we suggest that this score and its underlying model provide a tool that can usefully be put into clinical practice (Table 3).

While the other two models are guidelines for the use of prophylactic antiemetics rather than genuine risk scores to estimate the probability of PONV, they were included in this comparison for the sake of completeness.[20 21] Unfortunately, it is not clear to what extent the weight attributed to their risk factors is based on multivariable analysis. Moreover, they are more complex than the simplified scores of Apfel and Koivuranta and their colleagues, they do not have better discriminating power and do not provide a calibration curve. In addition, they cannot be used for the cost-effective strategy suggested by White and Watcha (Table 3).[10 11] The overall weak performance may indicate that risk models based on personal conviction yields poorer results than risk scores where the evidence is based on conscientious multivariate analyses of thoroughly collected data.

It seems surprising that models with a higher number of predictors were not superior to those with few predictors. The main reason may be that there are some predictors (e.g. female gender) which appear to be fairly constant in every population and are therefore part of every model, while other predictors included in the more complicated models do not seem to have more general applicability. For example, one model considered orthopaedic procedures to be associated with odds ratios between 2.6 and 5.9,[17] while they had no significant effect on PONV in this data-set (Table 1). Another reason is that the increase in discriminating power with an additional predictor is relatively high when the first predictors are introduced in a model but decreases when four or five predictors are already present, so that further inclusion of predictors is not justified.[24]

We have demonstrated that the simplified models appear to be easily applicable and to provide a valid concept to predict the probability of PONV in individuals. However, none of the models is able to predict with certainty which individual will actually suffer from PONV. An experiment with a virtual population has shown that this limitation results from the fact that the odds ratio of the risk factors for PONV is at best in the range of 2–3 (when non-reproduced outliers are not considered).[24] Therefore, unless significantly stronger predictors are found which appear to be applicable to most centres, it seems unlikely that further risk scores will lead to significantly better predictions.

Despite the above-mentioned limitations, the simplified risk scores can provide a rational basis for an antiemetic strategy. In addition, they may be used for group comparisons of randomized controlled trials of antiemetic strategies.[22] If, for example, several risk factors have a tendency to be more frequent in one group than in the other, although not being statistically significant on their own, this may lead to a significantly different risk, as assessed by a scoring model. Thus, a more cautious interpretation of the results may be needed. On the other hand, when one risk factor is significantly more frequent in one group than in the other, although the overall risk is similar, this finding would be put into perspective. Therefore, we believe that validated scores predicting PONV should be used not only in clinical practice but also in demographic tables for group comparisons in randomized controlled trials.

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Depth of sedation in children undergoing computed tomography: validity and reliability of the University of Michigan Sedation Scale (UMSS)

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Background. Safe care of sedated children requires ongoing assessment of the depth of sedation to permit early recognition of progression to over-sedation. This study evaluated the validity and reliability of the University of Michigan Sedation Scale (UMSS) as a measure of sedation during procedures. The UMSS is a simple observational tool that assesses the level of alertness on a five-point scale ranging from 1 (wide awake) to 5 (unarousable with deep stimulation).

Methods. Thirty-two children aged 4 months to 5 yr (mean 1.5 yr), sedated for computed tomography (CT), were studied prospectively. The CT nurse assessed sedation using the UMSS before sedative administration and every 10 min thereafter. The child was videotaped during each assessment, and segments were edited and their order was randomized. Four nurses blinded to sedative administration viewed the segments and scored sedation using the UMSS. One of these nurses also scored sedation using a visual analogue scale (VAS) and another using the Observer's Assessment of Alertness/Sedation Scale (OAAS). To examine the test–retest reliability, 75 randomly selected video segments were viewed and scored on a second occasion.

Results. Changes in scores from baseline to discharge supported construct validity ($P<0.0001$). Criterion validity was demonstrated by significant correlations between the UMSS and the VAS and OAAS. There was good interobserver agreement between blinded observers' scores for each level of sedation and at discharge, and between blinded observers and the CT nurse for scores of 0 and 1 (lighter levels of sedation), but less agreement for scores 2 and 3 (deeper sedation) and discharge scores. Test–retest reliability was supported by agreement in the observers' UMSS scores.

Conclusion. The UMSS is a simple, valid and reliable tool that facilitates rapid and frequent assessment and documentation of depth of sedation in children.

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The increased use of sedation to facilitate diagnostic and therapeutic procedures in children has led to the provision of care by non-anaesthetists in many settings.[1–3] In response, a report from the Royal Colleges of Anaesthetists and Radiologists has emphasized careful titration of sedation depth to prevent excessively deep sedation and its associated risks by non-anaesthetists.[4] Furthermore, practice guidelines from the American Academy of Pediatrics (AAP) and the American Society of Anesthesiologists (ASA) have been developed to ensure consistent monitoring and care of sedated children regardless of who provides such care.[5] [6] These guidelines stipulate that the level of consciousness and responsiveness should be assessed regularly and documented until the sedated patient satisfies specific discharge criteria. Frequent monitoring should permit early recognition of a child's progression into deep sedation and appropriate escalation of monitoring.

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Accurate assessment of the depth of sedation requires a tool that is reliable and valid, yet is easy to use in the clinical setting. A variety of tools has been developed to assess the depth of sedation in both the research and the clinical setting.[7–15] Those scales that have been shown to be valid and reliable measures of sedation are somewhat lengthy[8–10] and, while useful as measures of sedation for research studies, they are cumbersome for frequent assessment of sedation in the clinical setting. The University of Michigan Sedation Scale (UMSS; see Appendix) was devised as a simple scale to facilitate the rapid assessment and documentation of the depth of sedation in all patients who receive a sedative agent for a diagnostic or therapeutic procedure. The purpose of this study was to evaluate the validity and reliability of the UMSS in a group of children undergoing sedation for a diagnostic procedure.

Methods

With approval from the Institutional Review Board at the University of Michigan and written consent from a parent or legal guardian, we studied healthy children (ASA I, II) aged 4 months to 5 yr who were scheduled to undergo sedation for an outpatient computed tomography (CT) procedure. Children who were severely medically compromised and those with moderate to severe cognitive impairment were excluded.

All children in this study received chloral hydrate 50–75 mg kg^{-1} orally, which is routine practice for outpatient CT at our institution. The paediatric CT nurse monitored all children throughout the procedure according to institutional sedation guidelines, which included pulse oximetry in all cases. The child's level of sedation was assessed and documented by the CT nurse before administration of the sedative agent and every 10 min after administration until the child was discharged, with the exception of the time during the CT scan, when the children were left undisturbed. The level of sedation was scored using the UMSS and proceeded with an assessment of the child's response to voice, light stimulation, such as stroking the face, and deeper physical stimulation, such as massaging the upper back or tickling the chest or axilla. A trained research assistant videotaped the child during each assessment. Children were discharged home when institutional discharge guidelines were met. Criteria for discharge included return to baseline vital signs and level of consciousness, ability to maintain a patent airway and the presence of protective airway reflexes (i.e. gag and swallow).

When all observations were complete, videotaped segments were coded and edited and their order was randomized. Four nurses, experienced in the care of sedated children and postanaesthesia recovery, independently viewed the videotapes and scored the level of sedation using the UMSS. To determine test–retest reliability, 75 randomly selected segments were viewed and scored on a second occasion, several weeks after the first session of observations. Additionally, one of the nurses observed all segments and assigned sedation scores using a 0–10 cm visual analogue scale (VAS; 0=awake and alert; 10=unarousable) that globally rates sedation, and another using the Observer's Assessment of Alertness/Sedation Scale (OAAS),[8] a sedation scale previously validated in children. Each of these nurse observers was blinded to the administration of sedative agents.

Statistics

All analyses were performed using SPSS software (SPSS, Chicago, IL, USA). Construct validity refers to the degree to which a tool actually measures the characteristic that it is intended to measure. In this case, scores were expected to increase after sedative administration and decrease over time before discharge. To evaluate the construct validity of the UMSS, the Wilcoxon signed rank test was used to evaluate the change in score over time after sedative administration. Criterion validity is the degree to which the measurement agrees with other approaches for measuring the same characteristic. To determine criterion validity, scores from the UMSS were compared with those from the VAS and OAAS. Because the metrics were different between the UMSS, VAS and OAAS, z-transformations of the scores were performed and comparisons were made using Spearman's rank order correlation coefficients (Spearman's ρ). Correlation coefficients and kappa (κ) statistics for levels of agreement were used to determine interobserver and test–retest reliability of the UMSS scores. The κ statistic is a measure of agreement that allows for observer variability for categorical data and corrects for chance levels of agreement.[16] Kappa values of 0.4 or greater were considered to provide acceptable agreement. Significance was accepted at the 5% level (i.e. $P<0.05$). Data are presented as mean (SD) where applicable.

Results

Thirty-two children, 4 months to 5 yr of age (mean 1.5 yr), were enrolled in this study. Validity and reliability analyses were based on 164 observations made throughout the care of these children during their sedation experiences. The mean time from sedative administration to the start of the procedure was 31 (SD 10) min (range 15–55). The mean duration of CT scan was 18 (10) min. The time to discharge varied: the mean time from administration of sedation to discharge was 71 (12) min (range 40–100) and from the end of the procedure to discharge it was 22 (7) min (range 10–35).

Validity

Construct validity was supported by the significant increase in sedation scores assigned by the blinded observers from baseline to 10, 20, 30 and 40 min ($P<0.0001$) and a significant decrease in scores from immediately after the procedure to 10, 20 and 30 min thereafter ($P<0.0001$) (Table 1). Criterion validity was supported by the excellent correlations between the UMSS and VAS scores ($r=0.955$, $n=164$, $P<0.0001$) and between the UMSS and OAAS scores ($r=0.929$, $n=164$, $P<0.0001$).

Reliability

Interobserver agreement data for each level of sedation defined on the UMSS and for discharge scores are presented in Tables 2 and 3. Agreement between the blinded observers was good for scores at each level of sedation and at discharge. Additionally, there was excellent agreement between the CT nurse and blinded observers for sedation scores of 0 and 1, but less agreement for scores of 2 and 3, and poor agreement at discharge. There was a significant correlation between UMSS scores of the blinded observers and the CT nurse (Table 4). However, the CT nurses' scores tended to be lower than the blinded observers' average scores 30 and 40 min from baseline and immediately after the scan to discharge ($P=0.02$ immediately after scan; not significant for all other assessment times) (Table 1). Test–retest reliability of the UMSS scores at each level of sedation was supported by the excellent agreement in the observers' scores between the first and second observations (range 67–100% agreement; $\kappa=0.687$).

Table 1 Sedation scores at 10 min intervals before and after CT scanning Data are presented as mean (SD) (median, interquartile range) *$P=0\ 02$ compared with CT nurse

	CT nurse	Blinded nurses
Baseline	0 (0;0)	0 15 (0 36) (0; 0.0)
10 min	0.9 (0 88) (1; 0 0)	1.01 (1 1) (1; 0 0)
20 min	2 (0.98) (2; 1 0)	1 97 (1 3) (2; 1.0)
30 min	2 27 (0 88) (3; 1.0)	2 6 (1 1) (3; 2 0)
40 min	2.6 (0 79) (3, 2.0)	3.1 (0.72) (3; 3 0)
Post Scan	1 97 (0.93) (2, 1 0)	2.6 (0.98) (3; 2.0)*
10 min	1.3 (0.72) (1; 1 0)	1.5 (0 98) (1; 1.0)
20 min	1.1 (0.76) (1; 0 5)	1.6 (1.03) (1; 1 0)
30 min	1 (1; 1.0)	1 75 (0 5) (2; 1 25)
Discharge	1.14 (0.76) (1; 1 0)	1.6 (1.07) (1; 1 0)

Discussion

One of the most important elements of monitoring children who are sedated for a diagnostic procedure is frequent assessment of the depth of sedation.[5 6 17] Children may move rapidly from lighter levels of sedation to deep sedation, so that escalation of monitoring and a greater degree of vigilance become necessary.[5] The practical aspects of repeated assessment of sedation require a tool that accurately detects changes in level of sedation and is reliable, yet is simple to administer and document without interfering with the procedure. The UMSS was devised as such a tool, and our study demonstrates that this scale has a high degree of validity in detecting changes in depth of sedation, as well as good interobserver reliability between blinded observers.

Several sedation scales have been devised and studied for use in the research setting and the intensive care unit, and for sedation during procedures.[8 18 12] The OAAS was designed to measure changes in level of alertness during procedures. However, its ability to capture the deep levels of sedation that are frequently encountered in the paediatric setting is somewhat limited.[8] The Neurobehavioral Assessment Scale and the Vancouver Sedative Recovery Scale (VSRS), on the other hand, provide more discriminating measures of the depth of sedation, with emphasis on the extreme ends of the scale.[9 18] Although validity has been established for each of these tools, their length and/or content preclude repeated use during procedures. Indeed, Macnab and colleagues have reported an average assessment time of 4 min for scoring the VSRS.[18] The UMSS was devised as a simple, efficient tool to assess the depth of sedation over the entire continuum from awake to

Table 2 Interobserver agreement for UMSS scores (total observations=164) *n* represents the range in number of observations scored at that level of sedation Data are range/median

UMSS score	Agreement between each blinded observer and the CT nurse (four comparisons)	Agreement between the four blinded observers (six comparisons)
0=awake/alert ($n=38$–45)		
Agreement	68–82/80%	87–90/91%
κ statistic	0 642–0.797/0.719	0 78–0 872/0 842
1=sleepy/responds appropriately ($n=46$–58)		
Agreement	52–69/60%	72–87/78%
κ statistic	0 384–0 543/0.496	0.557–0 734/0 677
2=somnolent/arouses to light stimuli ($n=13$–34)		
Agreement	30–53/48%	38–87/59%
κ statistic	0 341–0.391/0.347	0.229–0 73/0 483
3=deep sleep/arouses to deeper physical stimuli ($n=23$–31)		
Agreement	16–68/54%	48–78/55%
κ statistic	0 029–0 587/0 435	0 283–0.778/0.510
4=unarousable to stimuli ($n=0$–30)		
Agreement	0	27–100/47%
κ statistic		0.373–0 588/0 465

Table 3 Interobserver agreement for UMSS scores at discharge (total observations=32). *n* represents the range in number of observations scored at that level of sedation *One child was scored as UMSS 4 by all blinded observers. Data are range/median

UMSS score	Agreement between each observer and the CT nurse (four comparisons)	Agreement between the four blinded observers (six comparisons)
0=awake/alert (n=3–5)		
Agreement	60–80/60%	75–100/100%
κ statistic	0.604–0.868/0.658	0.708–1.0/0.837
1=sleepy/responds appropriately (n=10–15)		
Agreement	47–60/54%	69–90/79%
κ statistic	0.23–0.364/0.260	0.49–0.702/0.662
2=somnolent/arouses to light stimuli (n=2–8)		
Agreement	14–43/35%	25–86/50%
κ statistic	0.00–0.238/0.154	0.097–0.727/0.344
3 Deep sleep/arouses to deeper physical stimuli (n=1–8)		
Agreement	0	38–100/59%
κ statistic		0.507–0.868/0.589
4=unarousable to stimuli (n^*=1)		
Agreement	0	100%
κ statistic		1.0

Table 4 Spearman's correlation coefficients between the UMSS scores of the observers All correlations were significant ($P<0.001$, two-tailed)

	CT nurse	Observer 1	Observer 2	Observer 3	Observer 4
CT nurse	1.00	0.823	0.862	0.779	0.841
Observer 1	0.823	1.00	0.894	0.898	0.869
Observer 2	0.862	0.894	1.00	0.880	0.928
Observer 3	0.779	0.898	0.880	1.00	0.858
Observer 4	0.841	0.869	0.928	0.858	1.00

unarousable, as discussed and defined in the AAP and ASA guidelines.[5 6] This tool was intended to provide a standardized method for assessing sedation, primarily for areas where non-anaesthesia providers are caring for sedated patients.

There are several tests to determine the validity of an instrument, the most important of which, perhaps, is the measurement of construct validity. The construct validity of the UMSS as a measure of sedation was supported by the increase in sedation score after the administration of the sedative agent and the subsequent decrease in score as the sedative effects wore off. This measure of validity was strengthened by the fact that the independent observers were blinded to the timing of each videotaped segment relative to drug administration, thereby reducing the bias that may otherwise influence the sedation score. Additionally, the high degree of correlation between the UMSS scores and those of the VAS and OAAS demonstrates the criterion validity of the UMSS.

Our study found good agreement between the blinded observers' sedation scores as well as a high degree of test–retest reliability. Conversely, we found less agreement between the blinded observers' scores and those assigned by the CT nurse. The CT nurses' scores tended to be lower than those of the blinded observers from 30 min after drug administration to discharge. Although video recordings captured the nursing assessment and appropriate stimulation of the child, it is important to note that the blinded observers based their scores on these brief taped segments only, whereas the CT nurses may have incorporated other contextual indicators of the child's sedation course into their assessments. On the other hand, these findings may reflect a clinical bias towards underestimating the depth of sedation, perhaps to avoid escalation of monitoring or to expedite the discharge of children after the procedure. The emphasis on rapid patient turnover in busy radiology settings may, in some cases, influence patient assessment such that some children may be discharged prematurely. Indeed, Coté has previously alluded to, and cautioned against, a similar clinical bias towards liberalizing the definition of conscious sedation for the convenience of the practitioner.[19] These findings suggest that further education of non-anaesthesia caregivers may be necessary to ensure accurate and objective assessment of the depth of sedation. Additionally, in busy settings that require rapid patient turnover, the availability of a centralized recovery area, such as a postanaesthesia care area, may facilitate appropriate discharge criteria for all patients.

It has been recommended that sedative drugs administered by non-anaesthetists should have a wide margin of safety so that unintended loss of consciousness becomes unlikely.[4] All children in our sample received chloral hydrate in moderate doses because of its purported margin of safety. While the intent in each case was to produce moderate sedation, a significant number of children were observed to be deeply sedated, and even unarousable at one time-point or more during the sedation episode. All children were monitored with pulse oximetry according to institutional standards, and none required escalation of care during the study period. As we did not follow these children beyond discharge, it is unknown whether any child experienced an adverse event at home. These data highlight the importance of careful monitoring of all children, regardless of the sedative agent used or its route of administration.

While our findings suggest good overall validity and reliability of the UMSS, there was some variability between observers at moderate to deep levels of sedation. Such variability may limit the usefulness of the UMSS in research settings that require a high degree of precision, such as in rigorous pharmacological studies that compare the potency of sedative regimes. However, our data support the ability of the UMSS to capture changes in the child's depth of sedation, and can therefore provide a useful tool in busy clinical settings that require frequent and rapid sedation assessment.

Ongoing assessment of the depth of sedation is important for early identification of the patient's progression into deep sedation and the potential loss of protective reflexes. The tool used to assess sedation must be able to capture this progression sufficiently. This study demonstrates that the UMSS is a valid measure of depth of sedation and has good interobserver and test–retest reliability. The tool has good clinical utility in that scores can be readily assigned when frequent assessment is indicated. Although the AAP and ASA guidelines require ongoing assessment throughout the procedure, it is impractical to do this just before and during the diagnostic procedure itself, as Hatch and Sury have suggested.[20] During this time, when sedation may be deepest, continuous pulse oximetry, assessment of vital signs and, in some cases, capnography may facilitate the safe monitoring of the child.

This study has evaluated the validity and reliability of the UMSS as a measure of sedation in young children undergoing non-painful procedures. Extrapolation of these data to other settings, including painful procedures and other populations, requires further investigation.

Appendix

University of Michigan Sedation Scale (UMSS)

0	Awake and alert
1	Minimally sedated: tired/sleepy, appropriate response to verbal conversation and/or sound
2	Moderately sedated: somnolent/sleeping, easily aroused with light tactile stimulation or a simple verbal command
3	Deeply sedated: deep sleep, arousable only with significant physical stimulation
4	Unarousable

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Positive pressure ventilation during fibreoptic intubation: comparison of the laryngeal mask airway, intubating laryngeal mask and endoscopy mask techniques

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Background. The efficacy of delivery of mechanical ventilation through different airway devices during fibreoptic intubation is not known.

Methods. We compared the laryngeal mask airway (LMA[†]), intubating laryngeal mask (ILM) and endoscopy mask for positive pressure ventilation (PPV) during fibreoptic intubation. In 80 adult paralysed patients, fibreoptic intubation was performed during PPV using a combination of a size 3 or 4 LMA with a 6.0 mm nasal RAE tracheal tube (LMA3/4 group; *n*=22), a size 5 LMA with a 7.0 mm nasal RAE tube (LMA5 group; *n*=18), an ILM with an 8.0 mm special reinforced tracheal tube (ILM group; *n*=20) or an endoscopy mask (Patil mask) with a 7.5 mm standard tracheal tube (Patil group; *n*=20). The inspiratory and expiratory tidal volumes (*V*I and *V*E) with a ventilation pressure of 20 cm H_2O were measured using a pneumotachograph.

Results. Mean *V*E values during fibreoptic intubation in the LMA5 [5.3 (SD 1.5) ml kg^{-1}] and ILM [7.1 (2.3) ml kg^{-1}] groups were greater than in the LMA3/4 group [2.6 (1.0) ml kg^{-1}, $P<0.0001$]. The mean *V*E was greater in the Patil group [20.6 (4.9) ml kg^{-1}] than in the other three groups ($P<0.0001$). Gastric insufflation during intubation was more frequent in the Patil group (30%) than in the other three groups (4.5–5.6%) ($P<0.05$).

Conclusion. PPV is possible with the LMA, ILM or endoscopy mask during fibreoptic intubation. With an airway pressure of 20 cm H_2O, ventilation during intubation using a size 3 or 4 LMA was almost insufficient, while ventilation using a size 5 LMA or an ILM was almost acceptable. Ventilation during intubation with the endoscopy mask was greater than that with the LMA or ILM, but gastric insufflation was more frequent.

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The laryngeal mask airway (LMA[†]) and intubating laryngeal mask airway (ILM) can aid management of the difficult airway as a ventilatory device and as a conduit for fibreoptic intubation.[1–5] Positive pressure ventilation (PPV) can be applied during fibreoptic intubation to reduce the potential risk of hypoxaemia.[2–5] Maintaining PPV during intubation is desirable in patients with an unexpectedly difficult airway, so we should know how well the LMA and ILM allow PPV during fibreoptic intubation. We studied the abilities of the LMA and ILM to allow PPV during fibreoptic intubation in comparison with that of the endoscopy mask.[6–8]

[†] LMA® is the property of Intavent Limited

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Methods

Patients

After approval of the study by the institutional ethics committee (Moji Rosai Hospital Medical Ethics Committee), written informed consent was obtained from all patients. Patients with pharyngeal pathology, significant lung disease, morbid obesity or known difficult intubation and those at risk of aspiration were excluded. Eighty ASA physical status I or II patients who required general anaesthesia and tracheal intubation for elective surgery were allocated randomly into one of three groups using the closed envelope method. At the preoperative visit, the Mallampati class was assessed.[9] In each patient, fibreoptic intubation was carried out while continuing PPV using an LMA (LMA group; *n*=40), ILM (ILM group; *n*=20) or endoscopy mask (Patil-Syracuse mask clear, Patil mask; Anaesthesia Associates, San Marcos, CA, USA) (Patil group; *n*=20). For intubation using a size 3 or 4 LMA, a 6.0 mm internal diameter tracheal tube should be used and for a size 5 LMA a 7.0 mm internal diameter tracheal tube is recommended.[2–4] The size of the tracheal tube used will affect the ability to deliver PPV, and 40 patients in the LMA group were subdivided into an LMA3/4 (size 3 or 4 LMA) and an LMA5 (size 5 LMA) group.

Equipment and preparation

In the LMA and ILM groups, the size of the LMA and ILM was selected according to recent recommendations (size 3 for small females, size 4 for females and small males, size 5 for males).[3 10] We used an appropriate size of nasal RAE tracheal tube[11 12] (Mallinckrodt Medical, Athlone, Ireland) for intubation in the LMA3/4 and LMA5 groups, respectively because of its adequate length. An 8.0 mm internal diameter special straight, silicone wire-reinforced, cuffed tracheal tube[3 5 10] (ILM Endotracheal Tube; Euromedical, Kedah, Malaysia) was used in the ILM group. A 4.0 mm outer diameter fibreoptic laryngoscope (FOL; Olympus, Tokyo, Japan) was used in the LMA3/4, LMA5 and ILM groups to obtain adequate air flow around the fibrescope.[4] A second 5.0 mm, 6.0 mm internal diameter uncuffed tracheal tube or a special stabilizing rod (ET Stabilizer; Euromedical) was used as a stabilizer for the removal of the size 3 or 4 LMA or size 5 LMA or ILM, as appropriate.[3 10] In the Patil group, for intubation with a modified endoscopy mask technique,[6 8] a Patil mask was prepared as follows. A lubricated 7.5 mm internal diameter standard tracheal tube (Sheridan, Kendall Company, Mansfield, MA, USA) was passed through the diaphragm of the Patil mask port to about 10 cm. A fibreoptic swivel connector was attached to the tracheal tube adapter, and the side arm of the fibreoptic connector was blocked with tape. The modified Ovassapian intubating airway with a black line on the pharyngeal surface[13] was used because this modification is useful when oral fibreoptic intubation is unexpectedly difficult. A 5.0 mm outer diameter fibreoptic bronchoscope (FOB; Olympus) was used in the Patil group to prevent difficulty in advancing the tracheal tube over the fibrescope by reducing the size gap between the fibrescope and the tracheal tube.[6] A water-soluble lubricant was used for all devices.

Anaesthetic management

All patients received our customary premedication with hydroxyzine 25–50 mg and atropine 0.25–0.5 mg i.m. 30 min before induction of anaesthesia. In the operating room, the patients were monitored with an electrocardiogram, indirect blood pressure, pulse oximeter and capnograph After preoxygenation for a few minutes, anaesthesia was induced with propofol 2 mg kg^{-1} and fentanyl 1 μg kg^{-1} i.v. Neuromuscular block was produced with vecuronium 0.1–0.15 mg kg^{-1}. Anaesthesia was maintained with propofol 5–10 mg kg^{-1} h^{-1} throughout the study period. The patient's lungs were ventilated with 100% oxygen through a standard face mask for 5 min.

Placement of the airway devices

After paralysis had been confirmed with a nerve stimulator, the allocated airway device was inserted in the LMA and ILM groups, fixed using a standard method according to the manufacturer's instructions,[3 10] and connected to the anaesthesia breathing circuit. Oropharyngeal leak around the LMA or ILM cuff was detected by noise during manual bag ventilation,[14 15] and the leak pressure at which the leak occurred was measured. If airway obstruction or a large leak was noted during manual ventilation, the LMA or ILM was replaced, or a different size was used. When manual bag ventilation was almost acceptable but the leak pressure was less than 15 cm H_2O, steady pressure was applied to the neck with the palm of an assistant's hand during ventilation and intubation to reduce the leakage.[16] In the Patil group, a modified Ovassapian intubating airway was inserted into the mouth. The Patil mask, previously fitted with the tracheal tube, was placed over the face with the distal 4 cm of the tracheal tube inserted into the airway. Gauze packing was used to facilitate a tight mask fit in edentulous patients if necessary. Then, the operator extended the patient's head and applied forward thrust to the jaw To maintain a constant airway opening and an adequate jaw thrust, a jaw support device[8 17] (JSD; Arizono Orthopedic Supplies Company, Kitakyushu, Japan) was applied to both angles of the jaw. A standard head strap was used to fit the mask. An anaesthesia breathing circuit was connected with the Patil mask using an elbow adapter.

The number of attempts at insertion was recorded for each airway device, and the time for insertion of the device from the insertion of the airway into the mouth to

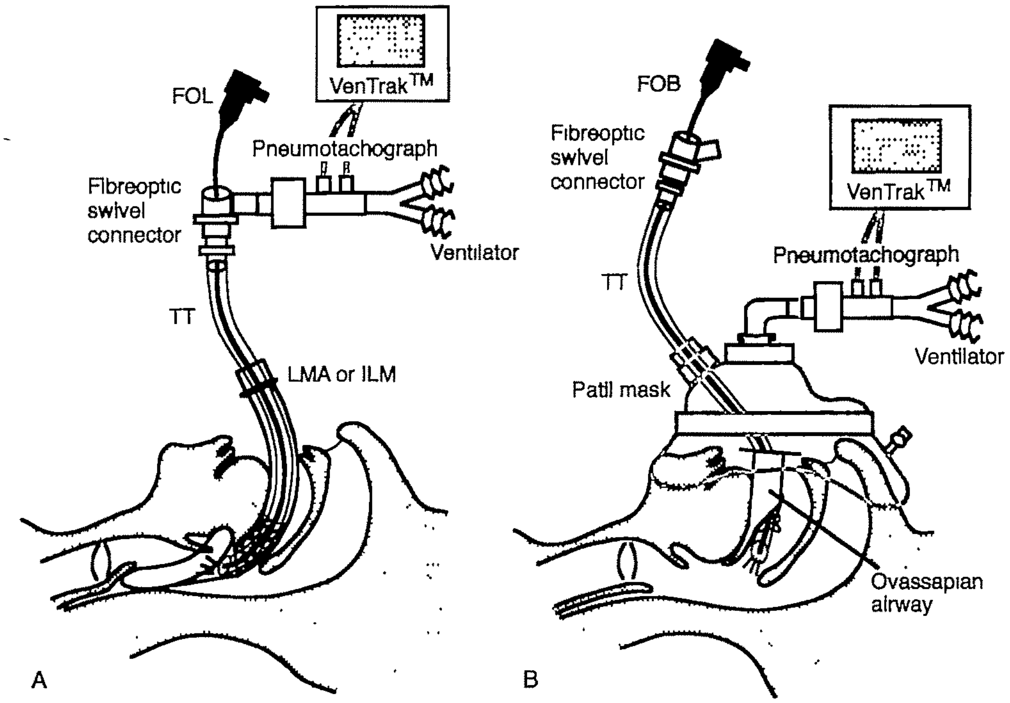

Fig 1 Fibreoptic intubation while maintaining positive pressure ventilation (PPV) and measurement of the tidal volumes with the laryngeal mask airway (LMA), intubating laryngeal mask (ILM) (A) or the Patil mask (B). (A) After insertion of an LMA or ILM, a 6.0 mm nasal RAE tracheal tube (TT) (LMA3/4 group), a 7.0 mm nasal RAE tracheal tube (LMA5 group) or an 8.0 mm special reinforced tracheal tube (ILM group) was inserted into the tube of the LMA or ILM. Fibreoptic intubation was performed while PPV was continued through the tracheal tube at a ventilation pressure of 20 cm H_2O. The inspiratory and expiratory tidal volumes (V_I and V_E) during fibrescopy (S_F stage) were measured with a pneumotachograph (VenTrak); the distal tip of the tracheal tube and the 4.0 mm outer diameter fibreoptic laryngoscope (FOL) were fixed at the LMA mask aperture bars or ILM epiglottic elevating bar during measurement. (B) After insertion of an Ovassapian intubating airway and placement of a Patil mask, fibreoptic intubation was performed while PPV was maintained through the Patil mask (Patil group). The side arm of the fibreoptic connector was blocked with tape.

completion of insertion (until cuff inflation of the LMA or ILM) was measured using a stopwatch in each group.

Mechanical ventilation

After the confirmation of airway patency by manual ventilation, mechanical ventilation was started using a ventilator (Puritan-Bennett Ventilator 760; Nellcor Puritan Bennett, Pleasanton, CA, USA) in the pressure control mode with 100% oxygen. A ventilation pressure of 20 cm H_2O, a respiratory rate of 12 and an inspiratory:expiratory ratio of 1:2 were used in all groups.

Fibreoptic intubation procedure

Fibrescope-guided intubation was performed by an experienced anaesthesiologist (>100 uses of each technique) while mechanical PPV was continued with each airway device. A fibreoptic swivel connector was attached to the tracheal tube and ventilation was carried out through the tracheal tube during intubation (Fig. 1A). The fibrescope was advanced through the fibreoptic connector into the tracheal tube and through the glottis into the trachea. The tracheal tube was advanced over the fibrescope into the trachea. After the 15 mm adapter of the tracheal tube had been removed, the second 5.0 mm (LMA3/4 group) or 6.0 mm (LMA5 group) tracheal tube was connected to the proximal end of the intubated tracheal tube as a stabilizer. The LMA was slid over the tracheal tube until the tracheal tube was visible in the mouth. The intubated tracheal tube was held in the mouth, the second tracheal tube was removed and the LMA was removed over the tracheal tube.[3] In the ILM group, an 8.0 mm special tracheal tube was introduced into the ILM tube, a fibreoptic swivel connector was attached to the tracheal tube, and mechanical PPV was performed through the tracheal tube (Fig. 1A). After the fibrescope had been advanced through the fibreoptic connector into the tracheal tube, the operator advanced the tracheal tube and pushed the epiglottic elevator bar with the tracheal tube according to the manufacturer's instruction manual.[10] The tracheal tube and fibrescope were advanced together through the glottis into the trachea after the tracheal tube had been aligned with the glottis. When the tracheal tube was not aligned with the glottis, the fibrescope was advanced into the glottis and then the tracheal tube was advanced over the fibrescope into the trachea. With the use of a special stabilizing rod, the ILM

Table 1 Patient characteristics and results of airway insertion Values are mean (SD) and the number (percentage) of patients. LMA=laryngeal mask airway, ILM=intubating laryngeal mask *$P<0.001$ compared with the other groups, †$P<0.0001$ compared with the other groups

	Group				
	LMA (all)	**LMA3/4**	**LMA5**	**ILM**	**Patil**
Number of patients	40	22	18	20	20
Age (yr)	63 (16)	68 (15)	56 (15)	62 (13)	64 (16)
Weight (kg)	59 (13)	52 (9)	68 (10) *	57 (10)	58 (6)
Height (cm)	158 (10)	152 (9)	165 (6)*	157 (12)	156 (8)
Male, female	25, 15	7, 15	18, 0	14, 6	13, 7
Mallampati class (I, II, III)	32, 7, 1	18, 4, 0	14, 3, 1	15, 5, 0	15, 5, 0
Airway size (3, 4, 5)	6, 16, 18	6, 16, 0	0, 0, 18	4, 6, 10	
Number of insertion attempts					
1	38 (95%)			18 (90%)	20 (100%)
2	2 (5%)			2 (10%)	
Time for airway insertion (s)	10.2 (3.5)	9.8 (4.1)	10.7 (2.7)	10.7 (4.2)	5.6 (1.6)†
Leak pressure (cm H_2O)	21 (6)	21 (6)	21 (5)	29 (4)†	–

was removed as the LMA was removed.[10] In the Patil group, the tracheal tube and the connector were already in place and PPV was carried out through the Patil mask (Fig. 1B). The fibrescope was advanced through the fibreoptic connector into the tracheal tube and through the glottis into the trachea. The tracheal tube was advanced over the fibrescope into the trachea. The 15 mm adapter of the tracheal tube was then removed and the Patil mask and the Ovassapian airway were removed. In each group, the tracheal tube was advanced with rotation, but when the tracheal tube could not be advanced over the fibrescope, further tube rotation[6] and/or external neck manipulation was applied to align the larynx with the tracheal tube. Correct placement of the tracheal tube was confirmed by capnography and auscultation in all groups.

During fibrescopy, the degree of exposure of the larynx was assessed using the following classification scheme:[6 8] easy=good visualization of the glottis was obtained on initial introduction of the fibrescope, so that little or no manipulation of the tip of the fibrescope was necessary; moderately difficult=some manipulation of the fibrescope was required to see the glottis; difficult=extensive manipulation was required to visualize the glottis. The times required for fibrescopy and intubation were measured using a stopwatch. The fibrescopy time was the time from the insertion of the fibrescope into the fibreoptic connector to the passage of the fibrescope through the vocal cords. The intubation time was the time from the insertion of the fibrescope into the fibreoptic connector to correct placement of the tracheal tube into the trachea. The number of attempts at tube advancement over the fibrescope was recorded. In all groups, auscultation was performed at the stomach to detect gastric insufflation during intubation.[14 18]

Measurement of tidal volume

The inspiratory and expiratory tidal volumes (V_I and V_E) during fibreoptic intubation were measured using a pneumotachograph (VenTrak 1550; Novametrix Medical Systems, Wallingford, CT, USA) in each group. Before the intubation procedure started, V_I and V_E during fibrescopy (S_F stage) were measured with the tracheal tube and the fibrescope fixed to minimize the leak caused by manipulation of the tracheal tube and fibrescope (Fig. 1A and B). At this stage, the tracheal tube and fibrescope were inserted by an anaesthesiologist who was not the intubator. The tracheal tube and fibrescope were then withdrawn (the tracheal tube in the Patil group was still in place), and V_I and V_E were measured at four stages (three in the Patil group) during the intubation procedure: (i) during ventilation through the airway device (S_{airway} stage); (ii) through the tracheal tube passed into the LMA or ILM tube before insertion of the fibrescope (S_{TT} stage; this stage was not used in the Patil group); (iii) at fibreoptic intubation (S_{FI} stage); and (iv) through the tracheal tube after tracheal intubation (S_{after} stage). At the S_F, S_{airway}, S_{TT} and S_{after} stages, measurements were made over 30 s (six breaths) and the mean V_E was calculated for each patient. During intubation (S_{FI} stage), V_I and V_E were measured over the time for intubation and the mean V_E was calculated. The leak fraction $[(V_I-V_E)/V_I]$[4 15] was calculated for each patient at each stage. The pneumotachograph was calibrated for gas and its accuracy (±5%) was checked before and after the study.

Statistical analysis

All ventilatory recordings were stored in a VenTrak computer and analysed on a personal computer using Analysis Plus software (Novametrix Medical System). Data are presented as mean (SD) or median (range). Most continuous variables (age, weight, height, time for airway insertion, leak pressure and tidal volume) were analysed using one-way analysis of variance and the Tukey–Kramer multiple comparisons test. The ordinal data (Mallampati class, number of attempts at airway insertion and tube advancement, and fibreoptic view) or the times for fibrescopy and intubation were compared by means of the Kruskal–Wallis test. The χ^2 test was used for nominal data

Table 2 Details of fibrescopy and intubation Values are number of patients, percentages or median (range) LMA=laryngeal mask airway, ILM=intubating laryngeal mask, E=easy; M=moderately difficult; D=difficult $^{*}P<0.05$ compared with the other groups

	Group			
	LMA3/4	**LMA5**	**ILM**	**Patil**
Fibreoptic view				
E, M, D	20, 2, 0	15, 3, 0	15, 3, 2	16, 4, 0
Time for fibrescopy (s)	12 (8–17)	11 (6–16)	12 (8–85)	12 (7–35)
Time for intubation (s)	24.5 (20–30)	25 (15–120)	20 (12–100)	23 (15–90)
Number of attempts at tube advancement				
1	22 (100%)	14 (78%)	18 (90%)	19 (95%)
2		2 (11%)	2 (10%)	1 (5%)
3		2 (11%)		
Incidence of gastric insufflation	1 (4.5%)	1 (5.6%)	1 (5%)	6 (30%)*

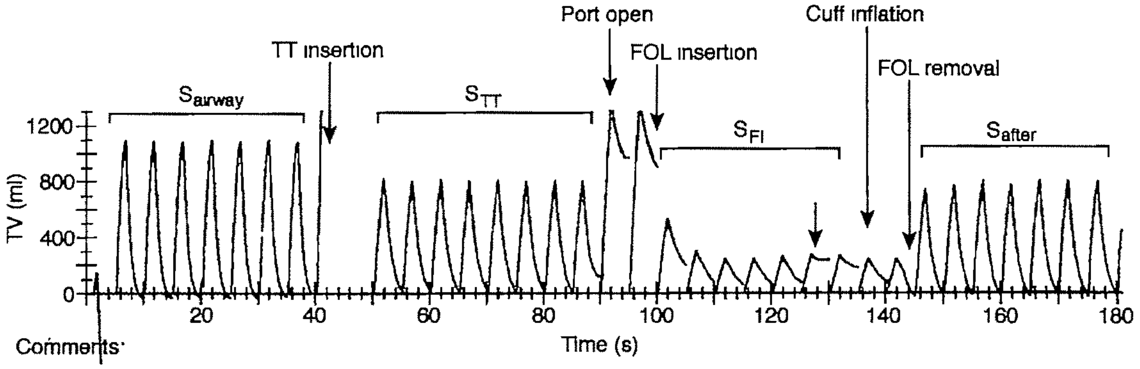

Fig 2 Typical traces of tidal volumes during fibreoptic intubation through the size 4 laryngeal mask airway (LMA) The inspiratory volume (V_I) trace is upwards After ventilation through the LMA (S_{airway}), a 6.0 mm nasal RAE tracheal tube was inserted into the LMA tube (TT insertion) and ventilation was performed through the tracheal tube (S_{TT}). A fibreoptic laryngoscope (FOL) was then introduced into the tracheal tube through the fibreoptic port (port open) and advanced into the trachea The tracheal tube was inserted into the trachea over the FOL During fibreoptic intubation (S_{FI}) in this patient, tidal volumes were measured over six breaths because the time for intubation was 33 s, and six volumes were averaged to obtain the mean V_E (mean V_E=194 ml in this patient). At the S_{FI} stage, leakage was noted after the tracheal tube cuff was passed below the mask aperture bars of the LMA (small arrow). Ventilation through the 6.0 mm RAE tracheal tube was adequate after the FOL had been removed (S_{after}).

(male/female distribution and incidence of gastric insufflation). A *P* value below 0.05 was considered statistically significant.

Results

The patient characteristics (Table 1) were similar for the three groups, but the LMA5 group differed from the other groups because of LMA size selection.

Insertion of the airway devices

The LMA, ILM or Ovassapian airway was quickly inserted in each patient (Table 1). There were no significant differences among the groups in the number of attempts at airway insertion (LMA, ILM or Ovassapian airway insertion). The leak pressure was higher in the ILM group than in the two LMA groups ($P<0.0001$). In four patients in the LMA3/4 and two in the LMA5 group, despite almost acceptable manual bag ventilation through the LMA itself, external neck pressure was applied by an assistant's palm to reduce leakage around the LMA cuff during fibreoptic intubation, because the leak pressure was less than 15 cm H_2O.

Fibreoptic intubation through each airway device

Fibreoptic intubation through the airway device was successful in all patients in each group. There were no significant differences among the four groups in the fibreoptic view, the time for fibrescopy and the time for intubation (Table 2). In some patients in the LMA5, ILM and Patil groups, the first tube advancement with rotation was halted at the level of the larynx, but the tracheal tube could be advanced successfully into the trachea by application of further tube rotation and/or external neck manipulation by an assistant. Gastric insufflation was more frequent in the Patil group than in the other groups ($P<0.05$). Haemoglobin oxygen saturation did not fall

Table 3 Inspiratory and expiratory tidal volumes at each stage during fibreoptic intubation. Values are mean (SD) LMA=laryngeal mask airway; ILM=intubating laryngeal mask; V_{I}=inspiratory tidal volume; V_{E}=expiratory tidal volume; S_{airway}=ventilation through the airway device; S_{TT}=ventilation through the tracheal tube (before fibrescope insertion); S_F=ventilation during fibrescopy (with the tracheal tube and fibrescope fixed); S_{FI}=ventilation during fibreoptic intubation; S_{after}=ventilation after tracheal intubation, Lf=leak fraction=(V_{I}–V_{E})/V_{I}. *$P<0.0001$ compared with the LMA3/4 group †$P<0.0001$ compared with the ILM group, ‡$P<0.0001$ compared with the other groups

Group	Stage S_{airway}	S_{TT}	S_F	S_{FI}	S_{after}
LMA3/4					
V_{I} (ml)	980 (209)	745 (75)	224 (27)	288 (58)	692 (116)
V_{E} (ml)	948 (214)	697 (101)†	176 (36)	128 (45)	675 (118)
Lf	0.03	0.06	0.21	0.56	0.02
LMA5					
V_{I} (ml)	1307 (158)	956 (67)	495 (57)	553 (49)	940 (114)
V_{E} (ml)	1280 (157)*†	921 (66)*†	464 (69)*	355 (68)*	923 (112)*
Lf	0.02	0.04	0.06	0.36	0.02
ILM					
V_{I} (ml)	1018 (272)	1096 (200)	844 (90)	873 (136)	1003 (223)
V_{E} (ml)	1003 (272)	586 (133)	432 (94)*	389 (93)*	995 (223)*
Lf	0.01	0.47	0.48	0.55	0.01
Patil					
V_{I} (ml)	1372 (255)		1382 (226)	1340 (253)	966 (210)
V_{E} (ml)	1261 (310)*†		1250 (299)‡	1188 (296)‡	958 (229)*
Lf	0.08		0.10	0.11	0.008

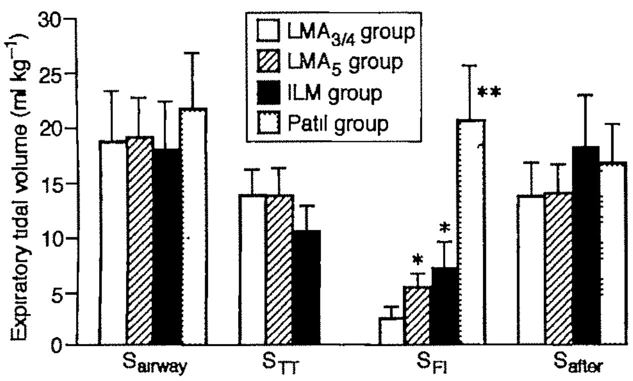

Fig 3 Expiratory tidal volume in relation to patient's weight (mean and SD) at four stages during fibreoptic intubation in each group. The four stages (three in the Patil group) of ventilation were ventilation through each airway device (S_{airway}); ventilation through the tracheal tube passed into the tube of the laryngeal mask airway or intubating laryngeal mask (S_{TT}), ventilation during fibreoptic intubation (S_{FI}); and ventilation through the tracheal tube placed in the trachea (S_{after}). Statistical differences are shown only for the S_{FI} stage. *$P<0.0001$ compared with the LMA3/4 group, **$P<0.0001$ compared with the other groups.

below 98% and end-tidal carbon dioxide did not exceed 40 mm Hg in any patient during the study period.

Expiratory tidal volume during intubation

Typical traces of tidal volumes through the size 4 LMA at the S_{airway}, S_{TT}, S_{FI}, and S_{after} stages are shown in Figure 2. At the S_{FI} stage, the tidal volumes were measured over two to 24 breaths according to the intubation time. At the S_{FI} stage in the LMA3/4 and LMA5 groups, a leak was noted after the tracheal tube cuff had been passed below the mask aperture bars of the LMA (Fig. 2, small arrow). The mean V_{I}, V_{E} and leak fraction at five stages in each group are presented in Table 3. The mean V_{E} values in relation to patient's weight at the S_{airway}, S_{TT}, S_{FI}, and S_{after} stages are shown in Figure 3. A mean V_{E} of more than 10 ml kg^{-1} was obtained at the S_{airway}, S_{TT} and S_{after} stages in most patients in all groups. The mean V_{E} values at the S_F and S_{FI} stages in the LMA5 [S_F 6.8 (SD 1.5), S_{FI} 5.3 (1.5) ml kg^{-1}] and ILM [S_F 7.9 (2.4), S_{FI} 7.1 (2.3) ml kg^{-1}] groups were greater than those in the LMA3/4 group [S_F 3.4 (1.3), S_{FI} 2.6 (1.0) ml kg^{-1}] ($P<0.0001$). The mean V_{E} values at the S_F and S_{FI} stages were greater in the Patil group [S_F 21.6 (4.9), S_{FI} 20.6 (4.9) ml kg^{-1}] compared with the other three groups ($P<0.0001$).

Discussion

During fibreoptic intubation, continuous PPV was possible through the LMA, ILM and endoscopy mask. From the tidal volumes obtained in the present study, ventilation during intubation using a size 3 or 4 LMA was insufficient, whereas ventilation using a size 5 LMA, ILM or endoscopy mask technique was almost satisfactory. The ability to deliver PPV during fibreoptic intubation depends on the space available for air flow and the effectiveness of each device in providing an airtight seal. With the LMA and ILM, PPV during intubation is performed through the tracheal tube inserted into the LMA or ILM tube. Thus, the largest size of tracheal tube that can be inserted into the LMA or ILM shaft should be used to ensure adequate air flow within the tracheal tube and to minimize leakage from the space between the tracheal tube and the LMA or ILM tube.[4]

Therefore, we used a tracheal tube with internal diameter 6.0, 7.0 and 8.0 mm for intubation with a size 3 or 4 LMA, a size 5 LMA and an ILM respectively. In addition, a longer tracheal tube is required for the LMA technique to allow the tracheal tube cuff to pass completely between the vocal cords.[2–4] We used a nasal RAE tracheal tube[11 12] because it is long enough. This tube, with proper lubrication, could be inserted easily into the LMA tube and into the trachea, and the bend of the tube did not cause any problem.[11 12] To obtain adequate air flow within the tracheal tube around the fibrescope, a 4.0 mm outer diameter FOL was used in the LMA3/4, LMA5 and ILM groups.[4] If a larger fibrescope is used, air flow around the fibrescope (tidal volume) decreases. We believe that each of the devices we used is suitable for obtaining as great a tidal volume as possible and for easy fibreoptic intubation.

With fibreoptic intubation through a size 3 or 4 LMA, when a FOL was inserted into the 6.0 mm internal diameter tracheal tube, the free cross-sectional area around the FOL (space for air flow) was reduced, resulting in increased resistance. In addition, manipulation (advancement or rotation) of the FOL and tracheal tube during intubation (S_{FI} stage) caused a leak through the port of the fibreoptic swivel connector (around the FOL) and through the space between the tracheal tube and the LMA tube. After the cuff of the tracheal tube had passed through the mask aperture bars, the leak was increased because the seal between the tracheal tube cuff and the LMA tube was lost. Consequently, a mean V_E of only 2.6 ml kg^{-1} could be obtained during intubation (S_{FI} stage). The patients' breathing tidal volumes (lung inflation and deflation volumes) at this stage may be larger than the measured V_E to some extent because leakage may occur during expiration. To minimize the effect of this leak, we examined the V_I and V_E while the tracheal tube and the fibrescope were fixed (S_F stage) in each patient. Despite the small leakage at this stage, a mean V_E of only 3.4 ml kg^{-1} could be obtained. These results indicate that ventilation during fibreoptic intubation with a size 3 or 4 LMA is insufficient at a ventilation pressure of 20 cm H_2O. However, with the combination of a 4.0 mm fibrescope and a 6.0 mm RAE tracheal tube, fibrescopy and intubation through the size 3 or 4 LMA could be done quickly in all patients and the time range for these was very small. Oxygenation can probably be maintained for such times despite a small tidal volume.

With the size 5 LMA, ventilation during intubation was acceptable in most patients and was superior to that with the size 3 or 4 LMA. A combination of the size 5 LMA, the 7.0 mm internal diameter RAE tracheal tube and the 4.0 mm outer diameter FOL provided almost adequate space around the FOL for PPV. Therefore, if applicable, the size 5 LMA is preferable to the size 4 LMA for effective ventilation. With the size 5 LMA, however, more attempts at tube advancement were required because tube advancement was halted at the level of the larynx. This may be because of a larger gap between the 7.0 mm tracheal tube and the 4.0 mm outer diameter FOL. Although the gap may decrease with a larger fibrescope, adequate space for ventilation is also reduced and the tidal volume obtained may decrease. When tube advancement was halted at the larynx, tube rotation or aligning the larynx with the tracheal tube by external neck manipulation could overcome this problem. Acceptable ventilation could be maintained during the intubation attempts.

For adequate ventilation, correct placement of the LMA is essential to create an open airway and adequate seal around the neck. Although oropharyngeal leakage around the cuff can occur even when the LMA is properly placed, ventilation through the LMA is possible despite some leakage.[14 15 18 19] During intubation, insertion of the tracheal tube and the FOL increased the leak, which made ventilation inadequate or impossible despite previously acceptable manual ventilation through the LMA itself. In these patients, external pressure applied to the neck reduced the leakage around the LMA cuff,[16] which permitted PPV during fibreoptic intubation. By this manoeuvre, the leakage during ventilation through the LMA itself was smaller in this study than in previous studies.[14 18 19]

When the ILM was used, the seal around the cuff was adequate to deliver PPV during intubation without the need for external neck pressure, but some leakage between the ILM tube and the tracheal tube occurred (S_{TT} stage) even when the 8.0 mm internal diameter tracheal tube, i.e. the largest available special tracheal tube,[5 10] was used. Thus, tidal volumes (lung inflation/deflation volumes) may be larger than the measured V_E to some extent with the ILM. However, the V_E obtained during fibrescopy and intubation was clinically satisfactory [mean V_E 7.9 (2.4) ml kg^{-1} at S_F and 7.1 (2.3) ml kg^{-1} at S_{FI}]. When a smaller tracheal tube is used (a 7.0 or 7.5 mm internal diameter special tracheal tube is available), tidal volumes may be less because the space for air flow decreases and the leak around the tracheal tube increases.

In contrast to the LMA and ILM techniques, with the endoscopy mask PPV during intubation is performed through the mask, not through the tracheal tube. Therefore, the size of tracheal tube and fibrescope would not affect the air flow. A 7.5 mm internal diameter standard tracheal tube (31 cm in length) was used for the endoscopy mask technique, because a 7.0 mm (30 cm) or smaller tracheal tube is not long enough to manipulate the tracheal tube over the Patil mask. The height of the Patil mask is about 7 cm and a tracheal tube more than 30 cm long is required to completely insert the tracheal tube into the trachea over the Patil mask. Because a smaller fibrescope is not necessary for adequate air flow, a 5.0 mm outer diameter FOB could be used in the Patil group to prevent difficulty in advancing the tracheal tube over the fibrescope by reducing the size of the gap between the fibrescope and the tracheal tube.[6] With this technique, the Ovassapian intubating airway and the jaw thrust manoeuvre with the JSD maintained an open airway,[8] which provided adequate space to deliver PPV. Ventilation with the endoscopy mask technique was better than that with the LMA and ILM techniques. However, gastric insufflation during intubation at a ventilation pressure of 20 cm H_2O was most frequent with the endoscopy mask, although the extent of gastric insufflation in each group was unknown. This result is consistent with previous studies of mask ventilation.[18 19] Gastric insufflation during fibreoptic intubation with the LMA or ILM is less likely to occur because a considerable decrease in pressure across the smaller tracheal tube occurs with the FOL. With the endoscopy mask technique, ventilation pressures less than 20 cm H_2O may be sufficient. In our previous study,[8] a *V*E of about 10 ml kg^{-1} was obtained at about 15 cm H_2O ventilation pressure without gastric insufflation. Gastric insufflation, however, should be anticipated and monitored during intubation with either technique, especially when a long time is required for intubation.

In the present study, there were no significant differences in the ease of airway placement and ease of fibreoptic intubation among the groups. Ventilation during intubation with the endoscopy mask was better than that with the LMA and ILM techniques. Therefore, when mask ventilation is easy and an experienced assistant can help to fit a mask and to apply jaw thrust, the use of the endoscopy mask technique is reasonable.[20] However, if mask ventilation and tracheal intubation are difficult, the LMA or ILM technique should be selected. In unexpectedly difficult airway situations, an LMA can achieve rescue ventilation reliably.[2–4 21] After ensuring ventilation through the LMA, tracheal intubation through the LMA, whilst PPV is maintained, is desirable.[3 4] Although ventilation during intubation with the size 3 or 4 LMA is insufficient, oxygenation can probably be maintained for a short time. If more ventilation is required, a higher respiratory rate should be applied to increase minute ventilation. Higher ventilation pressure may also be applied with the LMA technique because of a decrease in pressure across the smaller tracheal tube with the FOL. If applicable, the use of a size 5 LMA is preferable to a size 3 or 4 for effective ventilation. The recently introduced ILM has the potential to play an important role in airway management.[3 5] Satisfactory ventilation through the 8.0 mm tracheal tube and the ILM during intubation could be obtained in the present study. In some patients, however, the view of the glottis was poor, which prolonged fibrescopy and intubation. In addition, we have reported a case in which ventilation through the ILM was difficult because of partial airway obstruction caused by the fixed length of the rigid metal airway tube.[22] In some emergency situations, the standard LMA may be superior because of its flexibility. Further studies are required to establish the usefulness of the ILM for patients with a difficult airway.

The limitation of our study is that patients with a difficult airway, lung disease or morbid obesity were not included for ethical reasons. Our results may not always apply to these or critically ill patients, although the haemoglobin oxygen saturation and the end-tidal carbon dioxide were maintained within normal ranges in our healthy patients during the short study period. Tidal volume may be less in patients with obesity, decreased lung compliance or increased airway resistance, but our results may provide a useful comparison with ventilation during fibreoptic intubation using each technique.

We conclude that ventilation can be applied with the LMA, ILM and endoscopy mask throughout fibreoptic intubation. At a ventilation pressure of 20 cm H_2O, ventilation during intubation using a size 3 or 4 LMA was almost insufficient, and a higher respiratory rate should be applied to increase minute ventilation. Ventilation using a size 5 LMA or an ILM was almost acceptable, and the use of a size 5 LMA is preferable to a size 3 or 4 for effective ventilation, if applicable. Ventilation during intubation with the endoscopy mask technique was superior to that with the LMA or ILM, but gastric insufflation was more frequent. Careful choice should be made on the basis of other features of each technique in addition to the degree of ventilation.

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BJA

LABORATORY INVESTIGATIONS

Differential effects of intravenous anaesthetic agents on the response of rat mesenteric microcirculation *in vivo* after haemorrhage†

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Background. The differential effects of i.v. anaesthesia on the response of the mesenteric microcirculation after haemorrhage *in vivo* are previously unexplored.

Methods. Male Wistar rats (n=56) were anaesthetized intravenously either with propofol and fentanyl (propofol/fentanyl), ketamine or thiopental. A tracheostomy and carotid cannulation were performed and the mesentery surgically prepared for observation of the microcirculation using fluorescent *in vivo* microscopy. Animals were allocated to one of three groups: control, haemorrhage or haemorrhage re-infusion.

Results. After haemorrhage, the response of the microcirculation differed during propofol/fentanyl, ketamine and thiopental anaesthesia. During propofol/fentanyl anaesthesia there was constriction of arterioles (–16.7 (3.9)%), venules (–5.9 (1.7)) and capillaries (–16.3 (2.8)) (n=12). During ketamine and thiopental anaesthesia both constriction and dilation was observed. After haemorrhage and re-infusion, macromolecular leak occurred from venules during propofol/fentanyl and thiopental anaesthesia (P<0.05), but not during ketamine anaesthesia.

Conclusion. In summary, i.v. anaesthetic agents differentially alter the response of the mesenteric microcirculation to haemorrhage.

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The physiological response to haemorrhage involves tachycardia and generalized vasoconstriction.[1] The mesenteric microcirculation is particularly prone to intense vasoconstriction due to the dense supply of sympathetic nerves.[2] Thus, following haemorrhage the bowel is particularly susceptible to the secondary complications associated with haemorrhage, such as ischaemia.[3] The differential effects of intravenously administered anaesthetic agents on the response of the rat mesenteric microcirculation to haemorrhage have not previously been investigated. However, in dogs, the use of the i.v. agent propofol has been associated with low intestinal pH after haemorrhage, indicating ischaemia.[4]

It is well known that propofol and thiopental act centrally to inhibit the sympathetic nervous system, whereas ketamine has sympathomimetic actions.[5–7] It may be hypothesized, therefore, that these anaesthetic agents will also indirectly alter the response of sympathetically innervated arterioles (>18 µm) and venules (>30 µm) to haemorrhage.[1] Propofol, ketamine and thiopental have also been shown to possess direct locally mediated vasodilator properties, a response that appears to be mediated *via* inhibition of L-type voltage gated Ca^{2+} channels *in vitro*.[8–11]

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Previous studies performed in our laboratory have demonstrated differential responses to propofol/fentanyl, ketamine and thiopental anaesthesia with respect to the magnitude and incidence of small arteriolar (<25 µm) and venular (<30 µm) dilation.[12] These smaller vessels are influenced primarily by local control factors and may also respond differentially to haemorrhage during i.v. anaesthesia.[13]

Nitric oxide is a potent vasodilator and may also be affected by anaesthesia. Propofol has been shown to cause the release of nitric oxide by induction of nitric oxide synthase (NOS).[14] Nitric oxide is involved in maintaining blood flow in the mesenteric microcirculation after haemorrhage.[15] In contrast, vasodilation in response to the nitric oxide-donor sodium nitroprusside (SNP) appears to be reduced by propofol and this may be a mechanism by which propofol could potentiate vasoconstriction in response to haemorrhage.[16] Therefore, SNP will be used to determine how the *response* of the mesenteric microcirculation to nitric oxide is altered by i.v. anaesthesia.

In clinical practice, haemorrhage is usually treated by the re-infusion of fluid, which is associated with increased leakage of macromolecules in the gastrointestinal tract.[17] The presence of macromolecular leak is indicative of damage to the endothelium and compromised vessel integrity.[18 19] Macromolecular leak may pose a significant problem in the gastrointestinal tract, as this may be associated with the translocation of bacteria and the development of sepsis.[20] The effects of i.v. anaesthetic agents on macromolecular leak after haemorrhage have not previously been investigated.

The aims of this study, therefore, are to determine the effects of haemorrhage on the mesenteric microcirculation during propofol and fentanyl, ketamine and thiopental anaesthesia. *In vivo* microscopy has been used to study small arterioles, venules and capillaries and determine changes in vessel diameter and macromolecular leak.

Methods

Animals

Male Wistar rats weighing between 150 and 220 g (n=56) were obtained from the University of Sheffield Field Laboratories. All procedures were performed under the Home Office Animal Procedures Act (1986), Project Licence number 50/01252.

Anaesthesia and monitoring

Rats were placed in a restrainer and a paediatric butterfly needle inserted into the ventral tail vein to allow access for the induction and maintenance of anaesthesia with either: propofol (Diprivan, Zeneca Ltd, Macclesfield, UK) and fentanyl (Fentanyl Citrate, Janssen-Cilag Ltd, High Wycome, UK) (propofol 10–30 mg kg^{-1} induction, 10–50 mg kg^{-1} h^{-1} maintenance, fentanyl 6–8 µg kg^{-1} induction, 20–30 µg kg^{-1} h^{-1} maintenance); ketamine (Ketalar, Parke-Davis, Eastleigh, UK) (30–60 mg kg^{-1} induction 50–90 mg kg^{-1} h^{-1} maintenance); or thiopental (Intra-Vital Sodium, Rhone-Poulenc Rourer, West Malina, UK) (30 mg kg^{-1} induction, 40–90 mg kg^{-1} h^{-1} maintenance). Anaesthesia was induced at a steady rate over a 5-min period and maintained *via* 'step-down' continuous i.v. infusion (Graseby 3200 syringe pumps, Watford, UK). The doses used in this study were derived from doses described in the literature and refined in a series of preliminary studies. The infusion rate was adjusted to maintain a stable light plane of anaesthesia based upon the Lumb and Wynn Jones criteria.[21] Each animal exhibited a sluggish pedal withdrawal reflex, stable systemic arterial pressure, regular respiration rate and constricted pupils.

During anaesthesia, air containing 30% oxygen was introduced into a chamber surrounding the animal (1–2 litre min^{-1}) to ensure blood gases remained within the physiological range. Animals were placed on a warming pad to maintain body temperature between 36 to 38°C, which was monitored by an oesophageal thermistor probe and thermometer (Fluke, Washington, USA).

Surgical preparation

A tracheostomy was performed and a Portex cannula inserted to preserve the airway. A silicone cannula containing heparinized saline (100 Units) was inserted into the left carotid artery to allow continuous monitoring of cardiovascular variables via a pressure transducer and physiograph (Micro-Med, Louisville, USA).

The mesenteric surgical preparation was based on methods previously described.[22] In brief, a midline abdominal incision was made and the proximal end of the ileum and the adjoining mesentery were exteriorized. The tissue was kept moist with regular applications of warm saline and care was taken during handling to prevent physical damage. The area of interest was approximately 16–20 cm proximal to the ileocaecal valve (in a retrograde direction from the large intestine) and included 3–4 mesenteric windows. The tissue of interest was gently placed over the abdomen and the remaining intestine and mesentery were returned to the abdomen, which was then closed using a suture. Five stay sutures were then positioned at equidistant lengths along the avascular plane of the exteriorized ileum, with care taken not to perforate the small intestine. The animal was placed on its left side and the sutures used to firmly hold the mesentery flat on a microscope slide mounted on pillars on a Perspex board. The small intestine and mesentery were surrounded by gauze, moistened with warm (37°C) saline and covered with an impermeable membrane (Saran Wrap, Dow Chemical Co., UK) to prevent dehydration.

In vivo fluorescent microscopy

The animal and Perspex board, with attached warming pad, were transferred to the modified stage of an Optiphot-2 Nikon fluorescent microscope (Nikon Ltd, Kingston, Surrey, UK). This was equipped with a tungsten lamp for transmitted light and a mercury arc lamp for epi-illumination fluorescent light microscopy. A filter cube interposed into the path of a mercury arc lamp allowed blue light (450–490 nm) to be selected for epi-illumination of the mesenteric microcirculation. Fluorescein isothiocyanate (FITC) conjugated to bovine serum albumin (BSA) (FITC-BSA) is retained in the vasculature and epi-illumination with blue light results in green fluorescence, which allows the mesenteric microcirculation to be clearly visualized.[18] Images of the preparation were monitored using a CCD camera (Hitachi, UK), displayed on a high-resolution monitor (Sony, PVM-1443) and recorded by video (SLV-593, Sony, UK) onto tape (E-180 SX, JVC, Japan) for later off-line analysis. This included the addition of time and date information (DTG1, NG Systems, UK).

An area of the mesenteric microcirculation was recorded using epi-illumination to include an arteriole (10–25 μm), venule (15–30 μm) and 'capillary' (4–10 μm). These smallest vessels defined as 'capillaries' may have also included some pre-capillary arterioles and post-capillary venules. All vessels were located within the sub-mucosal mesenteric border.

Experimental protocol

Animals were allocated into one of the following experimental groups. 1. Control (C) (propofol, n=6, ketamine, n=6, thiopental, n=6). 2. Haemorrhage (H) (propofol, n=6, ketamine, n=7, thiopental, n=7). 3. Haemorrhage re-infusion (H–R) (propofol, n=6, ketamine, n=6, thiopental, n=6). C animals received i.v. anaesthesia alone. In the H group during anaesthesia, haemorrhage was induced by removing approximately 10% of the total body blood volume (actual volume=0.75 ml 100 g^{-1}) at a constant rate over a 10-min period (approx. 0.1 ml min^{-1}100 g^{-1}). No re-infusion was administered to the H group. However, in the H-R group, 30-min haemorrhage was followed by re-infusion of sterile saline and half the amount of blood removed during haemorrhage (saline: blood=2:1) at a steady rate over 10 min.

During the 30-min stabilization period (t=–30 to 0 min) areas were selected to assess microcirculatory variables and at t=0 min FITC-BSA 0.25 ml 100 g^{-1} was administered systemically *via* the carotid artery. This was followed by a 30-min baseline period (t=0–30 min) and an experimental period of 90 min (t=30–130 min) in all groups. In both the H and H–R groups, between t=30 and t=40 min, 10% haemorrhage was induced. In the H–R group, 30 min after haemorrhage, blood and saline were re-infused (t=70–80 min). In all groups at t=135 min, 1 ml of 10^{-5} M SNP (Sigma-Aldrich, UK) in saline was applied topically to the mesentery preparation to induce maximal dilation[23] Variables were then recorded immediately (t=135 min) and 15 min after application (t=150 min).

At the end of the experiment, 1 ml of blood was removed from all animals *via* a single use arterial blood sampling system (Concorde, Hythe, UK) for immediate analysis of blood gases ($P\text{O}_2$, $P\text{CO}_2$ and pH) (CIBA Corning, Medfield, USA). This sample was also used to determine haematocrit. A further 1 ml of blood was removed for later analysis of plasma anaesthetic concentration using standard high-pressure liquid chromatography and gas chromatography techniques.

Measurements

Temperature, cardiovascular and microcirculatory variables were measured over 30 s every 10 min for the entire 150-min experimental duration (t=0–150 min). Temperature, heart rate, systolic arterial pressure (SAP) and diastolic arterial blood pressure (DAP) were recorded on-line. Diameters of arterioles, venules and capillaries and macromolecular leak were assessed off-line using a Viglen IV/25 personal computer (Viglen, Middlesex, UK) and an image analysis software package (Image Pro Plus, Media Cyberkinetics, Silver Spring, Maryland, USA). External vessel diameter (including lumen and vessel walls) was measured in microns (μm). Macromolecular leak was assessed using the arbitrary grey scale to quantify interstitial FITC-BSA fluorescence. This was determined from the mean of three distinct areas (3 mm^2) adjacent to each arteriole, venule and capillary. Data for both variables are subsequently presented as a percentage change from t=30 min.

Statistics

All data were expressed as mean (SEM) Vessel diameters were expressed as a percentage change from t=30 min. After ANOVA, the Kruskall–Wallis and Mann–Whitney U-tests for non-parametric data were used to determine differences between the experimental groups for each anaesthetic agent. Within groups, variation was assessed using the Kruskall–Wallis test and the Wilcoxon test for paired data. All results were considered significantly different at P<0.05. A commercial software package was employed to determine r^2 values for the purposes of regression analysis and the relevant statistical tests performed using Minitab Inc., UK.

Results

Cardiovascular variables

In C animals, heart rate generally remained stable between t=0 min and t=130 min. SAP and DAP declined gradually

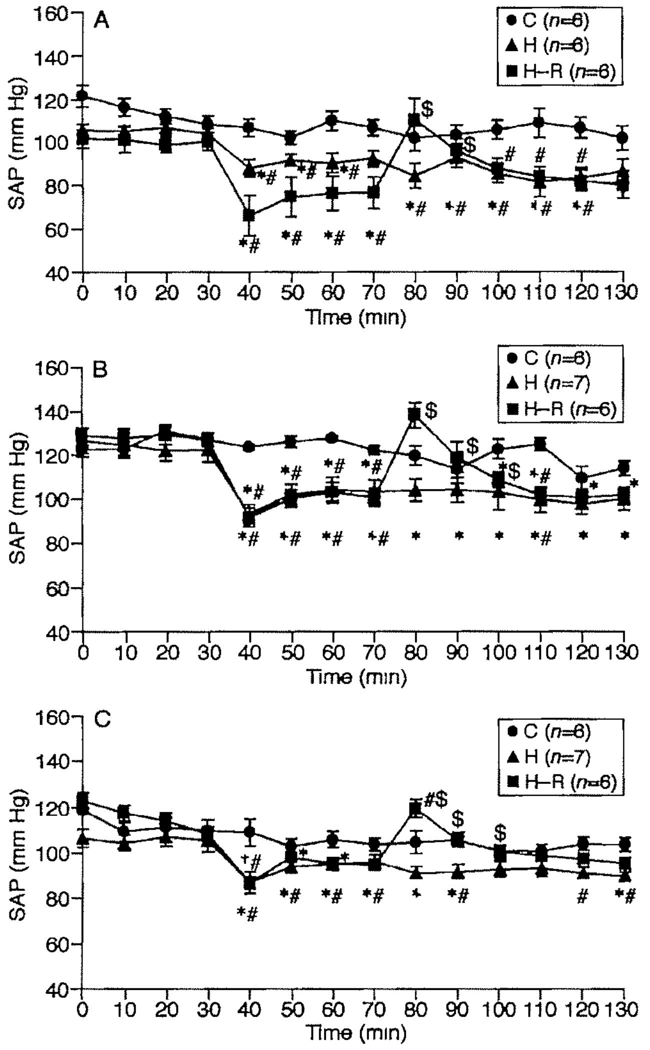

Fig 1 Systolic arterial pressure (SAP, mm Hg) in control (C), haemorrhage (H) and haemorrhage re-infusion (H–R) groups of animals during propofol/fentanyl (A), ketamine (B) and thiopental (C) anaesthesia. Haemorrhage occurred between 30 and 40 min and re-infusion between 70 and 80 min. $^*P<0.05$ significantly different from pre-haemorrhage (t=30 min) $^\#P<0.05$ significantly different from C. $^\$P<0.05$ significantly different from t=70 min (before re-infusion).

throughout the experiment (Fig. 1A–C). Between t=0 and t=130 min, SAP decreased by 27% (propofol/fentanyl), 7% (ketamine) and 13% (thiopental). After haemorrhage, a tachycardia was observed. During ketamine anaesthesia, a small increase in heart rate was observed from 433.1 (13.4) beats min^{-1} (t=30 min) to 460.8 (16.8) (t=40 min) (and H–R, n=13). Significant increases were observed from 434.0 (7.7) to 549.0 (33.3) during propofol/fentanyl anaesthesia ($P<0.05$, n=12) and from 389.5 (10.7) to 421.7 (10.3) during thiopental anaesthesia (n=13, $P<0.05$). Haemorrhage caused a significant decrease in SAP during propofol/fentanyl, ketamine and thiopental anaesthesia (Fig. 1A–C). DAP followed the same pattern. In H animals, the decrease in SAP and DAP was maintained for the remainder of the experiment.

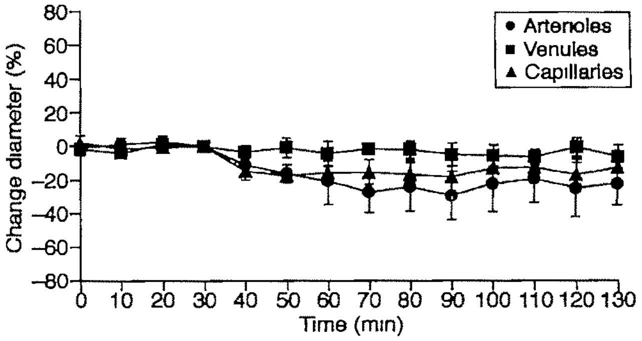

Fig 2 Percentage change in the diameters of arterioles, venules and capillaries in response to haemorrhage during propofol/fentanyl anaesthesia

In H–R animals, re-infusion caused a transient (10–20 min) increase in cardiovascular variables close to pre-haemorrhage and control values (t=80, 90), as demonstrated with SAP (Fig. 1A–C).

Vessel diameter

Prior to experimental manipulation (t=30 min), vessel diameters (μm) in all groups of animals (C, H and H–R) were 17.1 (0.9) (arterioles), 21.0 (1.3) (venules) and 8.0 (0.7) (capillaries) during propofol/fentanyl anaesthesia (n=18), 12.6 (0.5) (arterioles), 16.4 (0.8) (venules) and 7.5 (0.4) (capillaries) during ketamine anaesthesia (n=19) and 13.9 (0.6) (arterioles), 16.1 (0.9) (venules) and 7.5 (0.4) (capillaries) during thiopental anaesthesia (n=19). The diameters of arterioles and venules were greater during propofol/fentanyl anaesthesia, when compared with ketamine and thiopental ($P<0.05$).

In C animals, vessel diameters remained stable between t=0 and t=130 min with mean diameter changes for arterioles of −0.9(0.4)%, venules 1.4(0.5)% and capillaries −0.4(0.2)%, relative to baseline.

During propofol/fentanyl anaesthesia, after haemorrhage (t=40 min), there was constriction of arterioles (−16.7 (3.9)), venules (−5.9 (1.7)) and capillaries (−16.3 (2.8), n=12) (Fig. 2). At t=60 min the constrictor response was potentiated in arterioles (−29.2 (8.2)) and maintained in venules (−4.9 (3.7)) and capillaries (−16.4 (3.4)) (Fig. 2).

During ketamine anaesthesia, after haemorrhage (t=40 min) both constriction and dilation of arterioles (−11.3 (2.0); n=11, 22.0, n=2), venules (−5.6 (1.4); n=10, 10.5; n=3) and capillaries (−7.5 (1.6); n=6, 24.9 (6.5); n=7) was observed. At t=60 min these responses tended to diminish as vessel diameters returned towards values observed during the baseline period. During thiopental anaesthesia, after haemorrhage both constriction and dilation of arterioles (−20.3 (3.3); n=11, 3.9; n=2), venules (−7.9 (2.5); n=8, 3.7 (1.3); n=5) and capillaries (−12.8 (3.3); n=9, 4.7; n=2) was again observed.

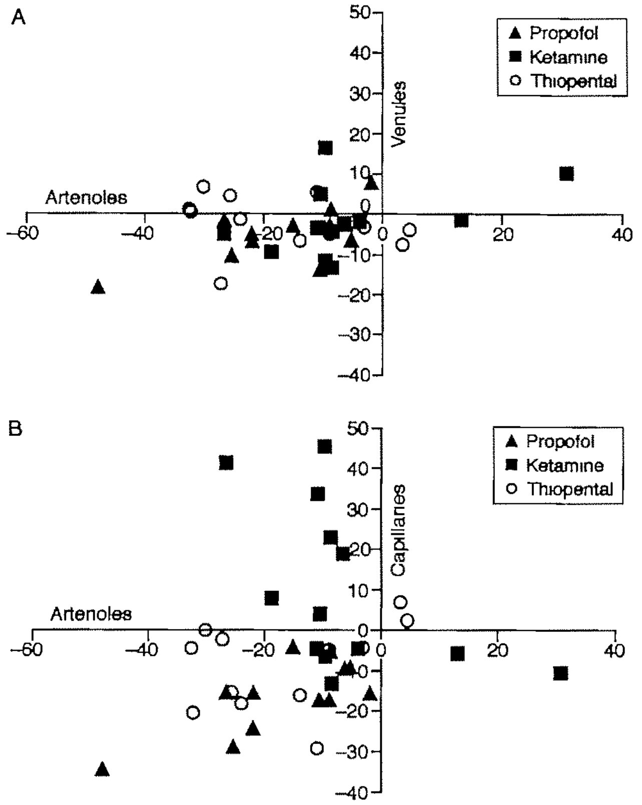

Fig 3 Percentage change in arteriolar diameter (x-axis) against the percentage change in diameter of (A) venules and (B) capillaries (y-axis) after haemorrhage ($t=40$ min) for H and H–R animals receiving either propofol/fentanyl, ketamine or thiopental anaesthesia.

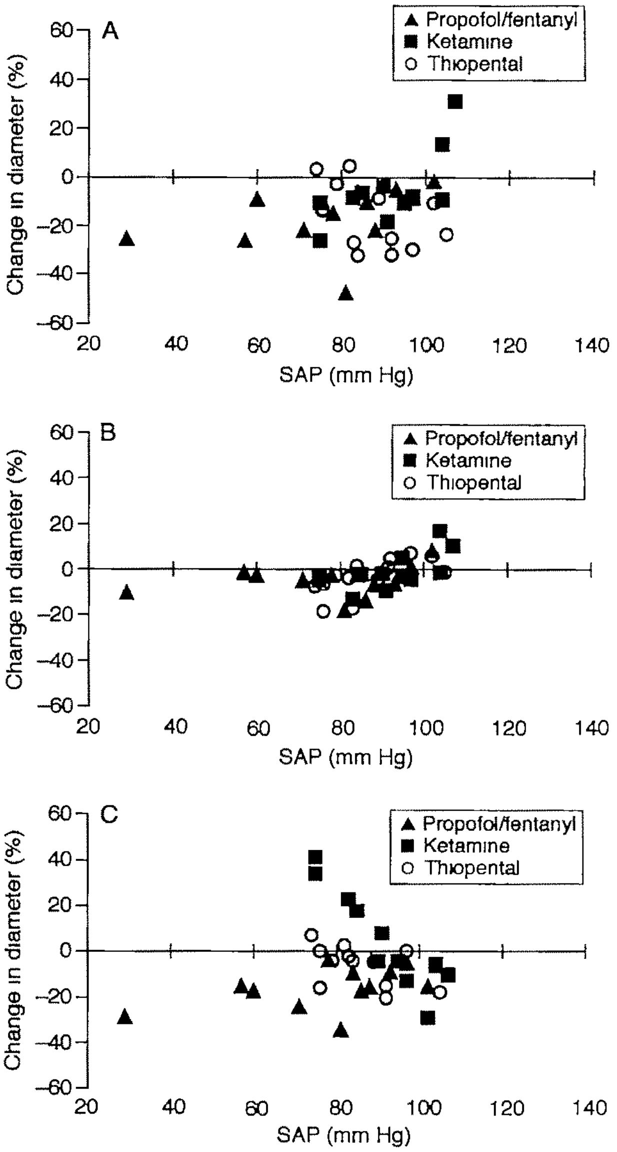

Fig 4 Systolic arterial pressure (SAP, mm Hg) *vs* percentage change in vessel diameter after haemorrhage ($t=40$ min) for (A) arterioles, (B) venules and (C) capillaries during propofol/fentanyl ($n=12$, H and H–R), ketamine ($n=13$, H and H–R) and thiopental ($n=13$, H and H–R) anaesthesia. A negative value indicates vessel constriction

The relationship between changes in arteriolar diameter in response to haemorrhage with the corresponding changes in venules and capillaries is shown in Figure 3 (A and B) for all animals (H and H–R) at $t=40$ min. Constriction of arterioles was generally accompanied by a smaller constriction of venules with all three agents, and this relationship was significant for propofol/fentanyl ($r^2=0.45$, $P<0.01$), but not ketamine and thiopental ($r^2=0.18$ and 0.08 respectively). However, arteriolar constriction was accompanied by a similar degree of capillary constriction during propofol/fentanyl anaesthesia ($r^2=0.54$, $P<0.01$) and to a lesser extent during thiopental (NS). During ketamine anaesthesia arteriolar constriction tended to be accompanied by capillary dilation ($r^2=0.27$, $P<0.05$). In all animals a similar pattern was still present at $t=60$ min (H and H–R before reinfusion).

In H–R animals, with all three anaesthetic regimens reinfusion caused a significant change in vessel diameters towards pre-haemorrhage values ($P<0.05$, $t=80$, 90). However, this change was transient and within 10–20 min vessel diameters returned to post haemorrhage values.

Systolic arterial pressure versus vessel diameter

To demonstrate the variation in vessel diameter response after haemorrhage SAP *vs* percentage change in diameter of arterioles, venules and capillaries for the three anaesthetic agents are compared in Figure 4A–C. In general, there was a constrictor response in all vessel types with decreasing SAP. However, a dilatory response was seen in arterioles during ketamine anaesthesia when SAP was maintained (NS) and also during thiopental anaesthesia when SAP was low ($r^2=0.42$, $P<0.05$). In capillaries, dilation was seen as SAP decreased with ketamine ($r^2=0.81$, $P<0.001$) and with thiopental ($r^2=0.41$, $P<0.05$). No dilatory responses were found with propofol anaesthesia. In venules, a relationship was identified between the decrease in SAP and the percentage change in diameter during ketamine ($r^2=0.39$, $P<0.05$) and thiopental ($r^2=0.42$, $P<0.05$) but not during propofol/fentanyl anaesthesia.

Table 1 Percentage change in arteriolar, venular and capillary diameter 5 min after topical application of sodium nitroprusside in control (C), haemorrhage (H) and haemorrhage re-infusion (H–R) groups during propofol/fentanyl (*n*=18), ketamine (*n*=19) and thiopental (*n*=19) administration. **P*<0.05 significantly different from the end of the experimental study period, #*P*<0.05 significantly different from C animals

	Arterioles	Venules	Capillaries
Propofol/fentanyl			
C	5.1 (1.5)	5.3 (2.7)	6.0 (1.9)
H	18.4 (5.9)*	7.2 (2.6)*	17.6 (4.7)*
H–R	13.4 (5.1)*	5.8 (2.3)	4.5 (2.1)
Ketamine			
C	7.9 (2.6)*	5.8 (2.7)*	17.0 (5.3)*
H	20.8 (7.9)*#	5.3 (1.3)*	13.7 (4.4)*
H–R	12.5 (4.4)*	6.0 (3.6)*	22.6 (12.3)*
Thiopental			
C	16.1 (5.2)*	6.1 (2.0)*	16.9 (4.9)*
H	13.1 (4.2)*	8.4 (3.9)*	17.0 (6.7)*
H–R	41.8 (19.5)*#	10.5 (3.2)*	0.8 (3.1)#

Sodium nitroprusside

In C animals, SNP caused significant dilation of arterioles venules and capillaries during ketamine and thiopental, but not propofol/fentanyl anaesthesia at *t*=135 min (Table 1, *P*<0.05). The greatest magnitude of response was observed in arterioles. Responses in arterioles were greater after haemorrhage during propofol/fentanyl and ketamine anaesthesia than in control animals (Table 1, *P*<0.05). Responses in arterioles were greater in H–R animals during thiopental anaesthesia than in C animals (Table 1, *P*<0.05).

Macromolecular leak

In C animals arterioles, venules and capillaries exhibited no significant increase in macromolecular leak between *t*=0 and *t*=130 min during propofol/fentanyl ketamine or thiopental anaesthesia (Fig. 5A–C). Haemorrhage did not induce a significant increase in macromolecular leak with any anaesthetic agent (Fig. 5A–C). Re-infusion after haemorrhage caused a significant increase in macromolecular leak from venules during propofol/fentanyl and thiopental, but not ketamine anaesthesia (Fig. 5A–C).

Blood gases

In C animals, $P\text{O}_2$, $P\text{CO}_2$ and pH were within the normal physiological range at the end of the experimental protocol during propofol/fentanyl, ketamine and thiopental anaesthesia (Table 2). After haemorrhage, however, pH was significantly lower in H than C animals during propofol/fentanyl anaesthesia (*P*<0.05). Haematocrit was lower in H than in C animals during ketamine anaesthesia (Table 2, *P*<0.05).

Plasma anaesthetic concentration

Plasma anaesthetic concentrations (µg ml^{-1}) were not significantly different between C, H and H–R groups for each anaesthetic agent. Propofol concentrations were 6.39 (1.08) (C), 6.69 (0.92) (H) and 6.53 (0.62) (H–R). Plasma ketamine concentrations were 0.75 (0.12) (C), 0.85 (0.14) (H) and 0.87 (0.12) (H–R). Thiopental concentrations were 62.7 (2.9) (C), 63.5 (2.4) (H) and 61.1 (2.9) (H–R).

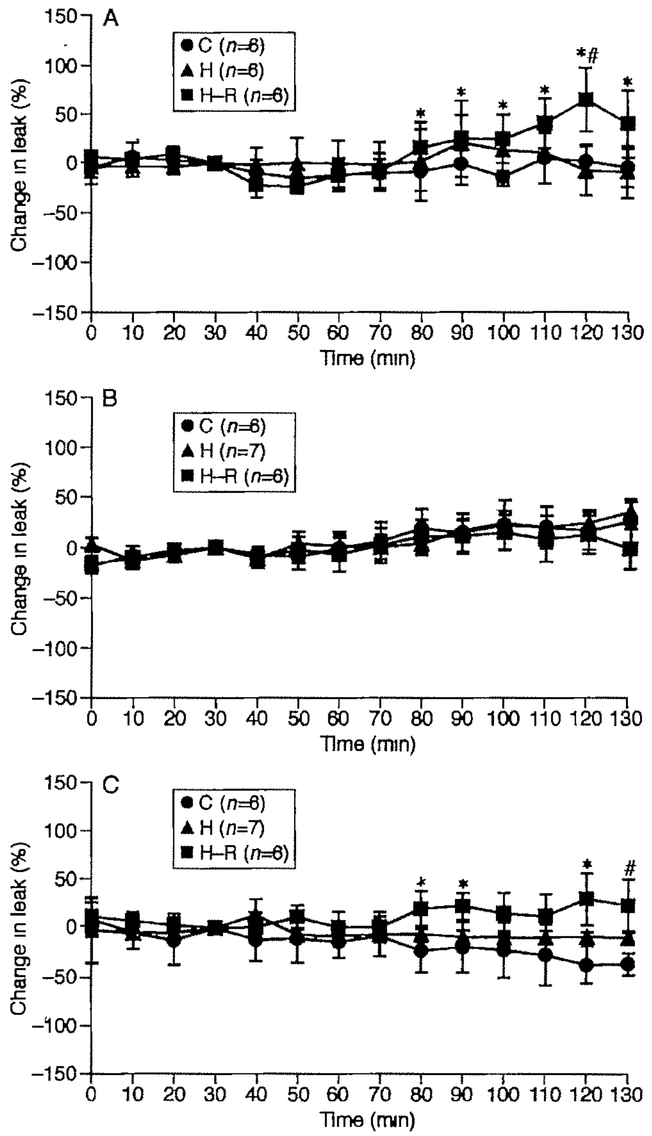

Fig 5 Percentage change in macromolecular leak in control (C), haemorrhage (H) and haemorrhage re-infusion (H–R) groups of animals during (A) propofol/fentanyl, (B) ketamine and (C) thiopental anaesthesia. Haemorrhage occurred between 30 and 40 min and reinfusion between 70 and 80 min. **P*<0.05 significantly different from pre-haemorrhage (*t*=30 min). #*P*<0.05 significantly different from C.

Discussion

This study has demonstrated for the first time that propofol/fentanyl, ketamine and thiopental differentially influence the response of the mesenteric microcirculation after haemorrhage. During ketamine anaesthesia, when SAP was maintained, dilation of mesenteric arterioles and

Table 2 Blood gases and haematocrit at the end of the experimental period, including $P\text{O}_2$ (kPa), $P\text{CO}_2$ (kPa) and pH in control (C), haemorrhage (H) and haemorrhage re-infusion (H–R) groups during propofol/fentanyl (n=18), ketamine (n=19) and thiopental (n=19) administration. *P<0.05 significantly different from C animals

	$P\text{O}_2$ (kPa)	$P\text{CO}_2$ (kPa)	pH	Haematocrit
Propofol/fentanyl				
C	15.70 (0.71)	4.79 (0.20)	7.34 (0.02)	0.40 (0.01)
H	17.22 (0.40)	5.14 (0.13)	7.28 (0.02)*	0.38 (0.02)
H-R	16.31 ±1.09	4.95 ±0.31	7.30 ±0.03	0.39 (0.01)
Ketamine				
C	15.76 (1.76)	4.85 (0.23)	7.35 (0.01)	0.42 (0.02)
H	15.34 (0.87)	5.10 (0.31)	7.35 (0.02)	0.38 (0.01)*
H–R	17.02 (1.25)	4.17 (0.29)	7.37 (0.02)	0.43 (0.01)
Thiopental				
C	14.57 (0.99)	5.20 (0.28)	7.36 (0.02)	0.44 (0.01)
H	14.38 (1.05)	5.14 (0.32)	7.34 (0.02)	0.42 (0.01)
H–R	15.81 (1.56)	5.04 (0.26)	7.35 (0.03)	0.42 (0.02)

venules was accompanied by constriction of capillaries. However, as SAP decreased, constriction of arterioles and venules was accompanied by dilation of capillaries. Different responses were observed during thiopental anaesthesia. At higher values of SAP there was constriction of arterioles and capillaries accompanied by dilation of venules, but, at lower pressures, arterioles and capillaries tended towards dilation and venules towards constriction. During propofol/fentanyl anaesthesia, SAP decreased in all animals and constriction of mesenteric arterioles, venules and capillaries was observed after haemorrhage. There was no evidence of a change in response at lower arterial pressures, as seen with thiopental.

Sympathetic nerves supply mesenteric microvessels to the level of terminal arterioles (>20 μm) and small collecting venules (>30 μm), thus, in the present study, constriction of vessels with similar diameters may have resulted from increased stimulation of the sympathetic nervous system after haemorrhage.[1] During propofol/fentanyl anaesthesia, the magnitude of constriction observed in arterioles and venules was greater at lower arterial pressures, accompanied by tachycardia, and probably associated with greater stimulation of the baroreceptor reflex.[13–24]

After haemorrhage, vasoconstriction of mesenteric vessels is a potential problem, increasing the risk of tissue ischaemia and gastrointestinal damage. In the current study, vasoconstriction was greatest during propofol/fentanyl anaesthesia. A greater decrease in systemic pH was observed after haemorrhage during propofol/fentanyl anaesthesia, compared with the other anaesthetic agents. This observation does not directly confirm mesenteric ischaemia, but indicates a generalized reduction in tissue perfusion and the occurrence of anaerobic respiration.[25 26] The vasoconstriction observed after haemorrhage during propofol/fentanyl anaesthesia could be an explanation for the decrease in local pH reported in previous studies.[4]

During thiopental anaesthesia, the degree of constriction of arterioles and capillaries appeared to decrease as SAP reduced, in contrast to the propofol/fentanyl study. This may reflect the fact that fewer animals had low SAP but could also show that the mechanisms maintaining arterial pressure were better preserved during thiopental anaesthesia. Lower arterial pressures after haemorrhage may have increased stimulation of the sympathetic nervous system and constriction of the mesenteric feeding arterioles (not measured), accompanied by reduced constriction and/or dilation of arterioles and capillaries to maintain adequate tissue perfusion. Mediators of vasodilation are probably not produced by the connective tissue of the mesentery, thus the observed vasodilation was probably myogenic in origin.[24] The vasodilator responses observed during thiopental anaesthesia may have reduced tissue hypoxia, and in agreement with this, systemic pH was maintained after haemorrhage. However, the reduction in both tachycardia and the vessel response to decreased SAP indicated a degree of baroreceptor reflex inhibition of sympathetic outflow by thiopental, in agreement with previous studies.[6 27]

During ketamine anaesthesia, dilation of arterioles and venules and constriction of capillaries occurred when arterial pressure was maintained. This was presumably due to sympathomimetic effects of ketamine, maintaining systemic arterial pressure after haemorrhage, with reduced sympathetic stimulation required to maintain SAP.[7] The vasodilator responses may have been myogenic in origin. For example, a decrease in intravascular pressure resulting from the decrease in systemic pressure and reinforced by constriction of larger arterial vessels may well result in myogenic dilation. The microcirculatory response to haemorrhage was altered at lower arterial pressures, with constriction of arterioles and venules accompanied by dilation of capillaries. Dilation of capillaries, when blood flow was decreased due to upstream vasoconstriction of arterioles, may have allowed the maintenance of local tissue perfusion. In the present study, this was confirmed by the maintenance of systemic pH with ketamine anaesthesia.[26] These observations are in agreement with previous studies in skeletal muscle, demonstrating well-maintained capillary perfusion with ketamine anaesthesia.[28] Constriction of arterioles and venules may have also maintained hydrostatic pressure and prevented fluid loss into the mesenteric extravascular space and hence, the abdomen. Interestingly, after haemorrhage fluid absorption appeared to be greater during ketamine anaesthesia,[29] as indicated in the present study by the greater decrease in haematocrit. Nevertheless, it would be expected that changes in capillary diameter are passive and their response should reflect upstream changes in blood flow. This was true during propofol/fentanyl and thiopental anaesthesia. Their response during ketamine anaesthesia however, confirms that perhaps some of the vessels described as 'capillaries' in this study were indeed precapillary arterioles, as these possess α_2 adrenoreceptors and thus may dilate in response to haemorrhage.[30] Dilation of precapillary arterioles would also have contributed to the maintenance of capillary perfusion previously described.

The infusion rate of each of the three agents was continually adjusted to achieve the appropriate plane of anaesthesia. The resulting plasma concentrations for each agent did not differ between the study groups suggesting that a constant level was achieved. The concentrations were within the range previously described for these agents in rats. Fentanyl was added to the propofol infusion protocol after our preliminary studies demonstrated that the dose of propofol alone required to maintain a suitable depth of anaesthesia for this study produced cardiovascular instability.

In control animals anaesthetized with thiopental, topical application of sodium nitroprusside (SNP) induced vasodilation in arterioles and capillaries, with a reduced response observed in venules. During propofol/fentanyl anaesthesia this response was inhibited, as arterioles and capillaries did not dilate in response to SNP. Thus, propofol/fentanyl anaesthesia may be inhibiting the *response* of the microcirculation to nitric oxide.[8] Alternatively, the absence of dilation may have been due to the vasodilator effects of propofol resulting in maximal vessel diameter.[8] Interestingly, our study demonstrated that arteriolar and venular diameters were greatest during propofol/fentanyl anaesthesia. Inhibition of the response to nitric oxide however, would confirm previous studies in the rat aorta *in vitro* whereby propofol was shown to inhibit vasodilation in response to SNP.[16] In the mesentery, nitric oxide is released in response to haemorrhage and assists with the maintenance of tissue perfusion.[15 31 32] Propofol may inhibit the *response* to nitric oxide *in vitro* and this mechanism could explain the observed increase in constriction after haemorrhage during propofol/fentanyl anaesthesia.[16] This hypothesis could not be confirmed in the present study as, after haemorrhage, SNP caused greater dilation of arterioles and capillaries than in control animals, indicating that the *response* of the mesenteric microcirculation to nitric oxide after haemorrhage is not inhibited by propofol/fentanyl anaesthesia.

This study has also demonstrated that macromolecular leak occurs in response to 10% haemorrhage when followed by re-infusion during propofol/fentanyl and thiopental anaesthesia, indicating compromised vessel integrity and damage of the mesenteric microcirculation.[15] Macromolecular leak has previously been reported in the mesentery, after ischaemia reperfusion injury.[19] Macromolecular leak was not observed in response to haemorrhage and re-infusion, during ketamine anaesthesia, perhaps indicating activation of a protective mechanism. It has previously been suggested that ketamine prevents leukocyte-endothelial interactions, which may be responsible for tissue and endothelial-cell damage.[33]

In conclusion, propofol/fentanyl, ketamine and thiopental have differential effects on the mesenteric microcirculation in response to haemorrhage, which relate to the decrease in systemic arterial pressure. The responses observed indicate that propofol/fentanyl promotes possible detrimental responses after haemorrhage, including greater decreases in SAP, systemic pH and increased mesenteric vasoconstriction. Ketamine, however, appears to exhibit a number of beneficial effects, including the maintenance of SAP, and the prevention of macromolecular leak after haemorrhage and re-infusion. In the present study therefore, ketamine appears to be the most suitable i.v. anaesthetic agent for use during haemorrhage.

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Xenon produces minimal haemodynamic effects in rabbits with chronically compromised left ventricular function

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Background. Xenon has only minimal haemodynamic side-effects on normal myocardium and might be a preferable anaesthetic agent for patients with heart failure. We studied the haemodynamic changes caused by 70% xenon in rabbits with chronically compromised left ventricular (LV) function.

Methods. Anaesthetized rabbits were thoracotomized and a major coronary artery was ligated to induce ischaemic heart disease. Nine weeks later, rabbits were again anaesthetized (ketamine/propofol), and haemodynamics were measured during inhalation of 70% xenon using echocardiography [LV end-diastolic dimension (LVedD), fractional shortening (FS), velocity of circumferential fibre shortening (VcF), ejection fraction (EF)] in closed-chest animals. Subsequently, rabbits were thoracotomized and instrumented for measurement of LV pressure (tip manometer), LV dP/dt_{max} and cardiac output (ultrasonic flow probe). Haemodynamics were recorded again during inhalation of 70% xenon.

Results. All rabbits had compromised LV function 9 weeks after coronary artery ligation. Mean LVedD increased from 12.9 (SD 0.9) mm to 17.1 (0.4) mm; EF decreased from 73 (9) to 64 (8)%; FS decreased from 36 (7) to 29 (5)%; VcF decreased from 28.9 (6.8) to 17.6 (4.7) mm s^{-1}; all $P<0.05$. Inhalation of 70% xenon had no effect on haemodynamics in closed-chest rabbits, as measured by echocardiography. After invasive instrumentation, small decreases in LV pressure from 78 (20) to 72 (19) mm Hg, LV dP/dt_{max} from 3081 (592) to 2633 (503) mm Hg s^{-1} and cardiac output from 239 (69) to 225 (71) ml min^{-1} were observed during xenon inhalation (all $P<0.05$).

Conclusion. These data show that xenon has only minimal negative inotropic effects in rabbits with LV dysfunction after coronary artery ligation.

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Keywords: anaesthetic gases, xenon; heart, left ventricular dysfunction; heart, myocardial function; monitoring, echocardiography

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The anaesthetic properties of xenon may make this noble gas an interesting adjunct to general anaesthesia. Several previous studies focused on the cardiovascular side-effects of xenon.[1–4] In humans, fractional area change obtained by echocardiography was not altered by 65% xenon.[1] No significant effect on arterial blood pressure could be observed in patients anaesthetized with 70% xenon in comparison with 70% nitrous oxide.[3] In pentobarbital-anaesthetized pigs, cardiac index, central venous pressure, aortic pressure (AOP) and systemic vascular resistance (SVR) were not significantly altered by 30–70% xenon.[5] During xenon anaesthesia, a tendency to decreased heart rate accompanied by an increased variability of the cardiac rhythm was observed.[1 2 6] Recently, we demonstrated by direct intracoronary administration in dogs that xenon has a small but consistent direct negative inotropic effect.[7]

The minimal cardiovascular effects of xenon are in contrast to the marked haemodynamic effects of other

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available inhalational anaesthetics. There are few data regarding the haemodynamic effects of xenon in pathophysiological myocardial conditions. Xenon reduced reperfusion injury after regional myocardial ischaemia in rabbits *in vivo*.[8] In isoflurane-anaesthetized dogs with dilated cardiomyopathy, addition of xenon decreased heart rate and increased the time constant of isovolumic relaxation.[9] In these experiments, no alterations of arterial or left ventricular (LV) pressures or indices of LV preload and afterload were observed.[9]

The current study investigates the haemodynamic changes during 70% xenon inhalation in rabbits with compromised LV function after ligation of a major coronary artery.

Materials and methods

The current study conforms with the Home Office Guidance on the Operation of Animals (Scientific Procedures) Act 1986, published by Her Majesty's Stationary Office in London, and was performed in accordance with the regulations of the Law on the Protection of Animals and local institutional regulations.

Induction of chronic LV dysfunction

New Zealand white rabbits were anaesthetized with intramuscular xylazine (6 mg kg^{-1}) and ketamine (6 mg kg^{-1}), followed by intravenous propofol (12 mg kg^{-1}). The trachea was intubated (tube 3.0 mm internal diameter) and the lungs were ventilated using a Harvard rodent ventilator (Model 683, Harvard, South Natick, MA) at a frequency of 30–35 bpm and a tidal volume of 15–20 ml in order to maintain end-expiratory CO_2 at approximately 35 mm Hg (Datex Ohmeda 5250 R6M, Division of Instrumentarium, Helsinki, Finland). Anaesthesia was maintained by inhalation of isoflurane (2–4 vol%) and nitrous oxide (50 vol%). Surface ECG was recorded continuously.

All surgical procedures were performed under sterile conditions, and intravenous antibiotic prophylaxis (cephazolin 35 mg kg^{-1}) was given. The chest was opened by a left thoracotomy in the fourth intercostal space, and a small incision made in the pericardium. The left anterior descending coronary artery was occluded with a 5-0 prolene suture (Ethicon 5/0, 1-metric, TF). The effectiveness of this manoeuvre was verified by the appearance of epicardial cyanosis and ECG changes. Ventricular fibrillation in the first 15 min after coronary artery occlusion was treated by electrical defibrillation (5 J, DCS261 Defibrillator, Piekser, Ratingen, Germany). Fifteen min after coronary artery occlusion, the chest wound was closed in layers and air aspirated from the thorax. Postoperative analgesia and antibiotic prophylaxis were given by subcutaneous injection of metamizole (30 mg kg^{-1}) and amoxicilline (15 mg kg^{-1}), respectively. A vest (rabbit jacket size M, Byron, Grand Island, NY) covered the wound.

Echocardiography

Before coronary artery occlusion and weekly thereafter, rabbits were anaesthetized with ketamine/xylazine and were allowed to breath spontaneously. The chest was shaved and animals were placed in the left lateral decubitus position on a warming pad to maintain normothermia.

Echocardiograms were performed with an HDI 3000 ultrasonograph (ATL, Solingen, Germany). A dynamically 5–8 MHz convex array transducer was placed on a layer of acoustic coupling gel applied to the left hemithorax. Short- and long-axis views of the left ventricle were obtained by slight angulation and rotation of the transducer. Two-dimensional targeted M-mode studies were obtained at the level of the papillary muscles. Anterior and posterior end-diastolic and end-systolic wall thickness and LV internal dimension were determined according to the leading-edge convention of the American Society of Echocardiography. LV fractional shortening (FS) was calculated as: FS = (EDD – ESD)/EDD where EDD and ESD represent LV end-diastolic and end-systolic dimension, respectively. Spectral Doppler waveforms were analysed for aortic, pulmonary artery, and peak early and late-diastolic transmitral velocities. Cardiac output (CO) was calculated echocardiographically from pulmonary artery flow. All measurements were made from original tracings and three beats were averaged for each measurement.

Invasive measurements

For measurement of AOP, a 20-gauge Teflon catheter was introduced from the left carotid artery into the aortic arch and connected to a pressure transducer (Statham transducer, PD23, Gould, Cleveland, OH). The external jugular vein was cannulated and animals received a continuous infusion of normal saline 15 ml kg^{-1} h^{-1} to compensate for fluid losses. After median sternotomy and pericardiotomy, an ultrasonic flow probe was placed around the ascending aorta in order to measure LV stroke volume minus coronary flow volume (4S ultrasonic flow probe, T 208, Transonic Systems Inc., Ithaca, NY). LV pressure was monitored using a catheter-tip manometer (Micro-Tip Pressure Transducer, SPC-350/5F, Millar Instruments, Houston, TX) introduced via the left atrium. After completion of the preparation, the thoracotomy was covered with plastic film to minimize evaporative and convective heat loss.

Experimental programme

Nine weeks after induction of chronic ischaemic heart disease, rabbits were anaesthetized with ketamine/xylazine followed by a continuous infusion of propofol (1.2 mg kg^{-1} min^{-1}) and were intubated and ventilated with 30% oxygen

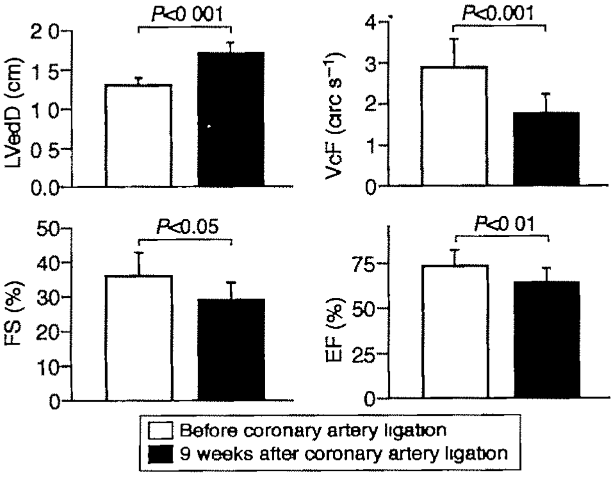

Fig 1 Bar plots showing left ventricular end-diastolic dimension (LVedD), fractional shortening (FS), velocity of circumferential fibre shortening (VcF), and ejection fraction (EF) before and after coronary artery ligation.

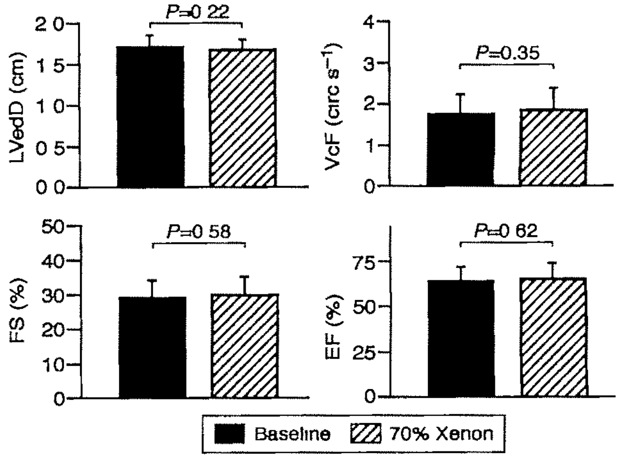

Fig 2 Bar plots showing left ventricular (LV) end-diastolic dimension (LVedD), fractional shortening (FS), velocity of circumferential fibre shortening (VcF), and ejection fraction (EF) in rabbits with chronically compromised LV function during baseline conditions and during inhalation of 70% xenon.

in air, as described above. Echocardiographic measurements were performed during baseline conditions and after 15 min inhalation of 70% xenon with 30% oxygen.

Fifteen min after completion of the preparation for invasive measurements, baseline values were determined and the rabbits again inhaled 70% xenon with 30% oxygen for 15 min. Another 15 min were allowed to wash out the noble gas and then isoflurane (1.2 vol%) was added to the inspired gas to ensure that the experimental model used was suitable to detect haemodynamic changes caused by inhalational anaesthetics.

At the end of the experiment, the heart was arrested by injection of potassium chloride solution into the left atrium, quickly excised and further processed to determine infarct size as described previously.[10]

Data analysis

LV pressure, its first derivative *dP*/*dt*, AOP, and stroke volume were continuously recorded on a personal computer (AcqKnowledge III, BIOPAC Systems Inc, Goleta, CA). Global systolic function was measured in terms of LV peak systolic pressure (LVPSP) and the first derivative of LV pressure, LV dP/dt_{max}. CO was calculated from stroke volume and heart rate, rate pressure product (RPP) from heart rate and LVPSP, and SVR from mean AOP and CO, assuming a right atrial pressure of 0 mm Hg in the open-chest preparation.

Measured values are presented as mean (SD). Statistical analysis was performed by Student's *t* test for paired observations (baseline values before and after coronary artery ligation and values before and after xenon inhalation). All comparisons were two-tailed and a *P* value <0.05 was regarded as significant.

Results

A total of 15 animals was used. Three animals died from recurrent ventricular fibrillation after coronary artery occlusion.

Development of LV dysfunction

Development of chronic LV dysfunction was measured weekly by echocardiography. Nine weeks after coronary artery occlusion, no further changes could be observed. Body weight increased during this time from 2.7 (0.3) to 3.3 (0.8) kg ($P<0.05$). Echocardiographic measurements showed an increase in LVedD and a decrease in myocardial function (Figure 1). Aortic flow velocity decreased from 96.4 (17.2) to 67.1 (12.9) cm s^{-1} ($P<0.05$) and CO (determined by echocardiography) from 226 (19) to 193 (36) ml min^{-1} ($P=0.14$).

Xenon in rabbits with LV dysfunction

No significant changes in global haemodynamics could be determined by echocardiography during inhalation of 70% xenon (Figure 2). After invasive instrumentation, xenon inhalation resulted in a small but consistent decrease of LV pressure, dP/dt_{max} and CO (Figure 3). Because heart rate did not change during xenon inhalation (baseline: 201 [23] beats min^{-1}; xenon: 202 [27] beats min^{-1}), RPP was altered in parallel to changes in LVP (baseline: 15.6 [4.6] mm Hg 10^3 min^{-1}; xenon: 14.5 [4.6] mm Hg 10^3 min^{-1}, $P<0.001$). Inhalation of 70% xenon had no effect on SVR (baseline: 274 [57] mm Hg min ml^{-1}; xenon: 264 [77] mm Hg min ml^{-1}, $P=0.5$).

To ensure that changes in haemodynamics could be determined with the method used, seven rabbits received

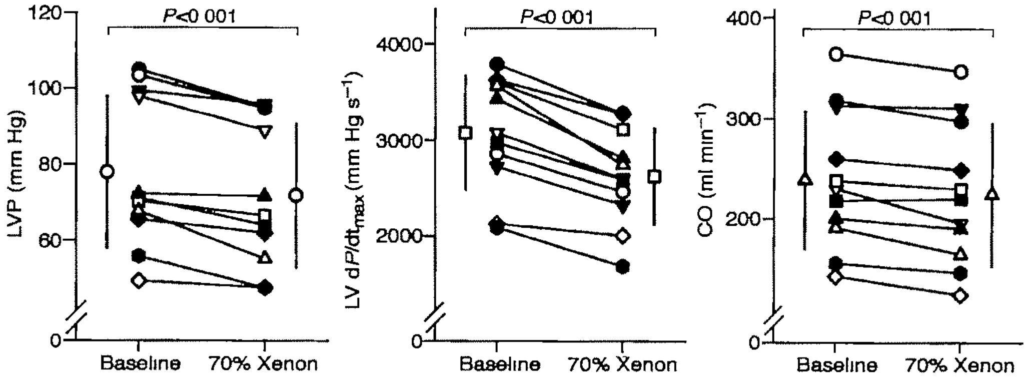

Fig 3 Line graphs showing left ventricular (LV) pressure (LVP), LV dP/dt_{max} and cardiac output (CO) for each experiment in rabbits with chronically compromised LV function. Measurements after invasive instrumentation were performed during baseline conditions and during inhalation of 70% xenon. Xenon produced a small but consistent decrease of LVP, dP/dt_{max} and CO

isoflurane 1.2 vol% at the end of the experiment. Inhalation of isoflurane produced a marked reduction of global haemodynamics by 18–44% of baseline values (Table 1).

Discussion

The main finding of the present study is that 70% xenon produces only minimal effects on cardiovascular function in rabbits with compromised LV function after chronic ischaemia. These findings underline the favourable haemodynamic profile of xenon – even in the presence of chronic ischaemic heart disease.

Critique of methods

Several methods have been described to induce heart failure in rabbits, such as chronic congestive heart failure after rapid ventricular pacing,[11] cardiomyopathy after adriamycin administration,[12] double pressure and volume overload[13] or permanent coronary artery occlusion.[14] We used ligation of a major coronary artery because ischaemic heart disease is the most common clinical cause for heart failure. However, with this model, only moderate LV dysfunction was achieved, as demonstrated by a decrease in myocardial function of 12–37% (Figure 1). Therefore, conclusions about haemodynamic stability during xenon inhalation must be limited to the situation of compromised LV function after coronary artery ligation. The effects of xenon on haemodynamics during severe congestive heart failure may be different. The site of coronary artery occlusion was the long axis of the left ventricle towards the apex approximately one-quarter of the distance from the atrioventricular groove to the LV apex. Increasing the size of the ischaemic area in this experimental model is not possible because a more proximal coronary occlusion results in unresolvable ventricular fibrillation and death.

Experiments were performed during baseline anaesthesia with ketamine and propofol. It cannot be excluded that, with different anaesthetic supplements or in other species, xenon may have different haemodynamic effects on failing myocardium.

We used xenon at a concentration of 70%. During inhalation and after recovery from xenon, no changes in arterial oxygen partial pressure were observed and it can therefore be concluded that hypoxia did not occur. Calzia *et al.* demonstrated that diffusion hypoxia is unlikely to occur during recovery from xenon anaesthesia.[15]

Only one concentration of xenon was used and the findings must be limited to this concentration. For the rabbit, the exact minimal alveolar concentration (MAC) has not yet been determined. In dogs, the MAC of xenon is superatmospheric at 119%[16] and in humans, 71%.[17] This MAC value has recently been confirmed in humans.[18] Taking the MAC values of the commonly used volatile anaesthetics in humans, dogs and rabbits, and relating these values to the MAC of xenon, it is likely that the MAC of xenon in rabbits is about120%. Therefore, 70% xenon might represent only 0.6 MAC in rabbits. The isoflurane concentration used is comparable to 0.6 MAC (2.0 vol% isoflurane = 1 MAC).[19]

Interpretation of results

Xenon can be used as an anaesthetic adjunct and it has been frequently reported that this noble gas produces only minimal effects on cardiovascular function. Our knowledge of the effects of xenon at the cellular and molecular level is still limited. Recently, Stowe *et al.* demonstrated that xenon does not alter cardiac function in isolated guinea-pig hearts.[20] In isolated cardiomyocytes, the amplitudes of the Na^+, L-type Ca^{2+}, and the inward-rectifier K^+ channels were not altered by xenon up to 80%. These data suggest that xenon does not affect the cardiac action potential In a previous study from our laboratory we showed that xenon, given directly to the myocardium by intracoronary administration, exerts a small but consistent direct negative inotropic effect in the dog heart *in vivo*, reducing variables of regional myocardial contractility by 5–8%.[7] However, these changes seemed to be negligible in comparison with

Table 1 Haemodynamic changes during inhalation of isoflurane 1.2 vol% in rabbits with chronically compromised LV function. Data are mean (SD), n=7, $^{*}P$<0.01; $^{**}P$<0.001 *vs* baseline LVP=left ventricular pressure, dP/dt_{max} and dP/dt_{min}=peak positive and negative velocity, respectively, of the change of LVP.

	Baseline	**Isoflurane**
Heart rate (beats min^{-1})	200 (20)	193 (9)
LVP_{max} (mm Hg)	64 (9)	46 (8)‡
dP/dt_{max} (mm Hg s^{-1})	3015 (672)	1690 (408)**
dP/dt_{min} (mm Hg s^{-1})	–2256 (388)	–1277 (310)**
Cardiac output (ml min^{-1})	193 (40)	153 (37)**
Systemic vascular resistance (mm Hg min ml^{-1})	295 (42)	241 (31)*
Rate pressure product (mm Hg 10^3 min^{-1})	12.7 (1.3)	8.8 (1.4)**

the inotropic changes caused by other volatile anaesthetics. In chronically instrumented dogs, cardiovascular stability was accompanied by an increase in total body oxygen consumption.[21] The increase in oxygen consumption was independent of the autonomic nervous system and might result from increased cell metabolism. In rats, the relationship between regional cerebral blood flow and cerebral glucose utilization is maintained during xenon anaesthesia, although reset at a higher level.[22] These data suggest that xenon increases organ blood flow. Myocardial blood flow was not measured in the present study; therefore, changes in myocardial oxygen delivery and consumption cannot be excluded.

Few data are available regarding the cardiovascular effects of xenon in pathophysiological states such as myocardial ischaemia or cardiomyopathy. In isoflurane-anaesthetized dogs with experimentally dilated cardiomyopathy, Hettrick and co-workers found that xenon had only minimal cardiovascular effects.[9] In these experiments, xenon decreased heart rate and increased the time constant of isovolumetric relaxation while having no effect on variables of preload and afterload. Xenon administration during reperfusion after coronary artery occlusion reduced myocardial reperfusion injury in rabbits.[8] In the presence of regional myocardial ischaemia and reperfusion, xenon produced a small reduction in CO and an increase in mean AOP, resulting in an increase in SVR.[8] This effect was rapidly reversible after discontinuation of xenon. In contrast, in healthy patients no haemodynamic changes during xenon anaesthesia as assessed by echocardiography were reported. The present data are in accordance with these previous findings, showing that the haemodynamic changes caused by xenon are too small to be detected by echocardiography (Figure 2). Invasive measurements revealed a slight negative inotropic action of the noble gas in rabbits with compromised LV function (Figure 3), but this effect was very small, at least in comparison with isoflurane (Table 1).

There is only one preliminary report of xenon used in cardiac-compromised patients.[23] Postoperative sedation with xenon/remifentanil in patients undergoing coronary artery bypass grafting resulted in haemodynamic stability (unchanged heart rate and mean arterial blood pressure), although cardiac index was slightly lower and SVR slightly higher compared with propofol/remifentanil sedation.[23]

In summary, our data show that xenon has minimal effects on global haemodynamics in rabbits with compromised LV function after coronary artery ligation. Because of its considerable cost and limited availability, xenon anaesthesia might not achieve widespread clinical use, but may be a useful alternative in selected patients. Xenon anaesthesia may be beneficial for patients with cardiac disease who cannot tolerate the depressant effects of other commonly used anaesthetics.

Acknowledgement

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BJA

REVIEW ARTICLE

Analgesia for pelvic brachytherapy

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Radiotherapy is an important and potentially curative treatment for malignancies of the cervix, endometrium, vagina, vulva, rectum, anus and penis. Successful treatment requires a combination of external beam x-ray and brachytherapy. Brachytherapy (brachy=short, therapy=treatment) is the placement of radioactive sources within the body cavities such as the uterus and vagina (intracavity brachytherapy), or within the tissues (interstitial brachytherapy). It allows an extremely high dose of radiation to be received by the tumour, with relative sparing of the surrounding tissues from radiation-induced complications.

The anaesthetist is a vital member of the brachytherapy team. Many of the patients are medically unfit for surgery. The radioactive sources are potentially very painful and can remain *in situ* for several days. During this time, the patient is nursed in an isolated room to reduce the radiation exposure to staff. The use of appropriate analgesic techniques can reduce these treatments from being an ordeal to slightly unpleasant.

Intracavity brachytherapy for cervical and endometrial cancers

Cervical cancer

Over the last 10 yr, cervical screening programmes and a rise in the standard of living has led to a fall in both prevalence and mortality from carcinoma of the cervix. In 1998, there were over 3500 new cases in the UK[31] and 13 700 cases in the USA.[22] However, it is still extremely common in the developing world where it is the most common female cancer.[29]

Stage 1B tumours (confined to cervix) can be treated by Wertheim's hysterectomy with cure rates of 85–90%. Patients considered unfit for surgery can be treated by radical radiotherapy with identical cure rates, but lower morbidity than surgery.[17] More advanced stage tumours are treated by radiotherapy. Since cervical cancer is relatively slow to metastasize from the pelvis, it is possible to cure 40% of stage 3B tumours (fixed to one or both pelvic side walls).[8] Recently, it has been shown that chemotherapy given along with pelvic brachytherapy reduces the risk of death by 30–50% compared to patients treated by radiotherapy alone.[36] This significant advance may increase the number of patients referred for radiotherapy.

Endometrial cancer

The treatment of choice for most patients with endometrial cancer is simple hysterectomy, with cure rates of 80–90% if the tumour is confined to the uterus.[1] In patients considered unfit for surgery, intracavity brachytherapy can result in a 5-yr survival of up to 73%.[14]

Intracavity brachytherapy techniques

Manually inserted radiation sources provide 'gold standard' treatment results at the expense of radiation exposure of staff. To reduce these risks, most centres in Europe now use remote after-loading systems. Aluminium and nylon applicators are inserted into the uterus and vagina under anaesthesia (Figs 1 and 2). Pneumatic hoses are connected to the applicators postoperatively, allowing stainless steel pellets (containing caesium in glass) to be moved in and out of the applicators from a computer-controlled lead safe. This can reduce the radiation exposure of nursing staff by 30-fold.[15]

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After-loading systems deliver radiation at either high dose rate (HDR) in just a few minutes or at low dose rate (LDR) over 15–72 h. In 1994, a survey of UK practice found 97% of all departments used LDR but 41% planned to introduce HDR machines.[13] HDR and LDR treatments have markedly different anaesthetic and analgesic requirements.

High dose rate

HDR treatment can be completed in a few minutes and performed on an outpatient basis. General anaesthesia, spinal anaesthesia[23] or conscious sedation with fentanyl and midazolam[33] are sufficient. Once the applicators are withdrawn, there are no further analgesic requirements.

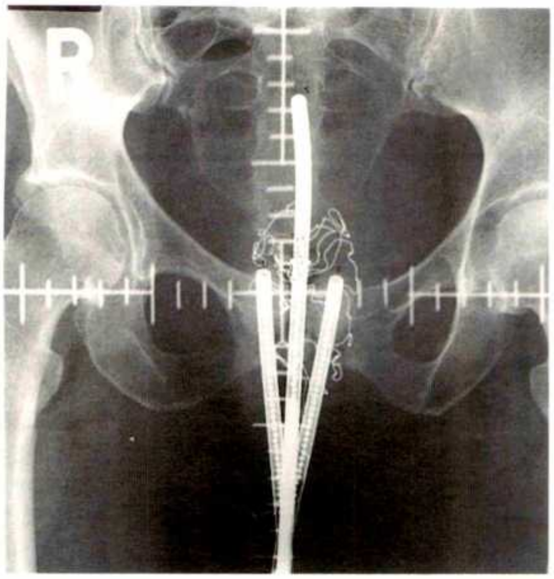

Fig 1 A–P radiograph of intrauterine/intravaginal insertion using selectron applicator.

Two methods have been described which avoid repeated anaesthesia for serial treatments. First, an indwelling cervical sleeve can be inserted under anaesthesia during the initial treatment. This can remain *in situ* to allow subsequent introduction of uterine applicators without anaesthesia. However, 26% of patients still experienced severe uterine pain which was relieved by nitrous oxide.[37] Second, osmotic dilators can be introduced to dilate the cervix 10–12 h before insertion of the applicators. Discomfort is minimal with fentanyl and midazolam supplementation.[18] Both methods are particularly useful in medically unfit patients.

Low dose rate

Following anaesthesia for insertion, the applicators remain inside the uterus and vagina for 15–72 h during LDR treatment. The postoperative care of these patients is complicated by many factors:

Patient characteristics

Typical patients presenting for pelvic brachytherapy vary from younger, fitter cases of cervical carcinoma (75% ASA I–II) to older, medically unfit cases of endometrial carcinoma (83% ASA III–IV).[29] The most striking feature in younger women is the marked anxiety and distress produced by the nature of the underlying condition.[34] In contrast, a series of 96 endometrial cases noted multiple risk factors (Table 1),[3] with another series noting an average body mass index of almost 50 kg m^{-2}.[24]

Type of pain

The cause of considerable discomfort is multifactorial. The presence of applicator rods in the body of the uterus stimulates sympathetic autonomic afferents which enter the spinal cord at the T10–L1 level. This produces poorly

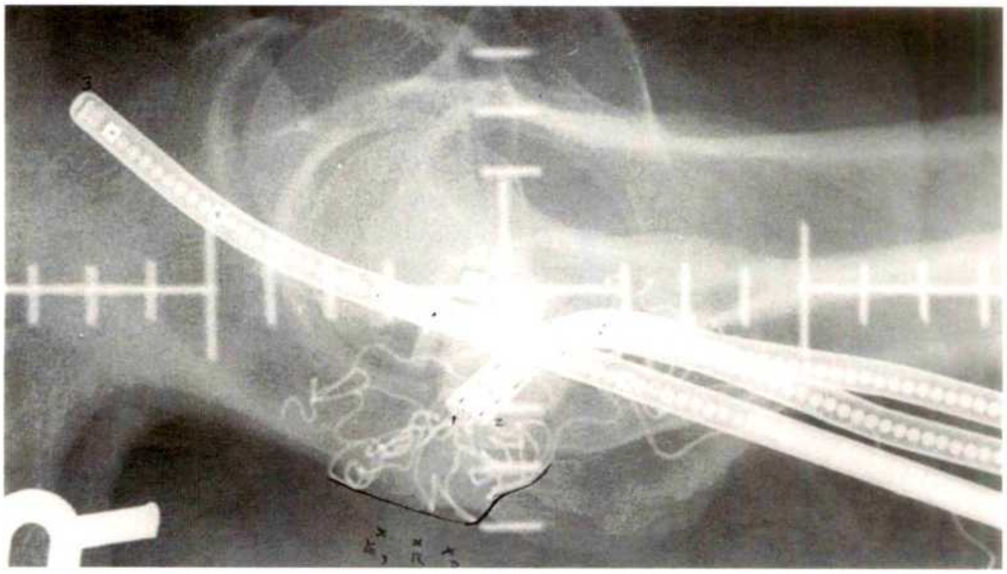

Fig 2 Lateral radiograph of intrauterine/intravaginal selectron insertion.

Table 1 Incidence of medical risk factors in patients with endometrial cancer

Risk factor	Incidence (%)
Hypertension	50
Age >75 yr	40
Morbid obesity	30
Diabetes mellitus	30
Congestive heart failure	20
Myocardial infarction	10
Thromboembolism	10
Cerebrovascular disease	10

localized, central, lower abdominal pain of a cramping nature associated with nausea and vomiting. Distension of the cervix and upper vagina stimulates parasympathetic autonomic afferents from the pelvic splanchnic nerves of S2–4 to cause lower back pain. Vaginal packing and its retaining suture through the labia stimulates somatic afferents *via* the pudendal nerves of S2–4. Patients have a urinary catheter, and a rectal marker is initially present until the correct position of the applicators is confirmed by postoperative x-ray. All these stimuli are considerably worsened by patient movement. This occurs on transfer from the operating table to the transfer trolley and bed, on attachment of pneumatic hoses from the after-loading device and the removal of applicators some 20 h later. During this prolonged treatment the patient must lie still in bed, which can result in considerable pain and stiffness in up to 80% of cases.[12]

Postoperative environment

This often comprises an isolated single room. Close supervision is severely limited by the need to avoid radiation exposure to staff. Adequate monitoring of pain and vital signs is hampered by the need to interrupt treatment for recordings, as well as by equipment and staffing levels on the ward.

Analgesia for low dose rate intracavity brachytherapy

There is little published evidence on analgesic techniques for LDR pelvic brachytherapy. What mention there is originates from the oncology literature and this probably reflects the relatively small numbers of patients managed in any particular unit. In light of the factors complicating postoperative care, the following analgesic options can be considered.

Inhalational analgesia

Inhalational analgesia from nitrous oxide is well suited for the short term discomfort of applicator attachment, patient movement or applicator removal (where there is a sudden increase in pain many hours after other modes of analgesia have ceased to have an effect).[37] It is easily administered, well tolerated and effective if used in anticipation of the stimulus.

Non-steroidal anti-inflammatory drugs and simple analgesics

Non-steroidal anti-inflammatory drugs (NSAIDs) and simple analgesics (including codeine phosphate as a routine constipating agent) contribute to a multimodal approach. In particular they may ease the cramping central abdominal pain, which many patients relate to menstrual pain. The use of NSAIDS may reduce the requirement for systemic opioids, as seen in other forms of gynaecological surgery.[21]

Systemic opioids

It is difficult to meet the wide variation in dose requirements *via* the intramuscular root (morphine requirements in young patients have exceeded 30 mg in the first 4 h of treatment in our unit). Such administration consumes a considerable amount of nursing time, frequently interrupts treatment and risks significant breakthrough pain. Patient-controlled analgesia (PCA) is a useful alternative in this setting, and its general advantages have been well described elsewhere. The degree of control given to the patient is helpful in enabling them to cope. Having a favourable respiratory depressant profile in comparison with other opioid techniques is a particular advantage in the isolated setting. Sedation, commonly referred to as a side effect, can be regarded as beneficial in such highly anxious patients. PCA requires regular monitoring assessments which interrupt treatment, unless remote alarmed monitoring is available.

As pelvic brachytherapy is a form of gynaecological surgery often performed on young women, it is no surprise to find that postoperative nausea and vomiting (PONV) can be problematic in the presence of systemic opioids. Although prophylactic antiemetics are of value,[16] the incidence of PONV in published series varies from 25 to 50%.[4 16 34] It occurs despite the avoidance of opioids and with the use of topical or regional anaesthesia for applicator insertion. In a study where systemic opioids were used, up to 47% of patients were not fit for discharge at the end of treatment due to PONV, dizziness and unsteadiness.[10] In our unit this is a particular problem when patients who require large amounts of PCA morphine are mobilized on the morning following treatment. We believe this to be exacerbated by perioperative dehydration. Patients are fasted for anaesthesia, and remain supine and potentially nauseous during 20 h of treatment, resulting in reduced oral intake for up to 32 h prior to mobilization. Routine perioperative i.v. fluids are recommended.

Sedation

Sedation, often with fentanyl and midazolam, although not strictly speaking an analgesic technique, is frequently utilized in HDR therapy.[24 33] In LDR therapy, benzodiazepines are often used to alleviate distress and promote sleep during protracted treatment in younger, more anxious patients.[12] Indeed, 21 h of target-controlled propofol sedation has been described.[26] This technique demanded considerable monitoring and staffing resources (comprising an anaesthetist with remote monitoring, continuously present in an adjoining room), which were only deemed justifiable in an exceptional case. There is a balance to be struck between opioid and benzodiazepine use which reflects individual patient requirements. Oncology nurses are particularly experienced in making this judgement.

Local anaesthesia

Paracervical block is mentioned in only a few cases with no real indication of its effectiveness.[18 20] The topical placement of 10% lidocaine 4 ml on the cervix and vagina has been evaluated in HDR therapy.[13] The reduction in visual analogue scores from 60 mm (SD 24.8) to 49. 9 mm (24.1) was significant. However, moderate pain still remained and the effects would not be of sufficient duration for LDR therapy.

Caudal epidural block

This is used in our unit. A standard approach with 0.375% bupivacaine 20 ml is well tolerated and produces minimal leg weakness. We are currently evaluating the contribution of the block due to the frequent requirement for supplemental opioids. This may be due to several factors. From the innervation of the structures involved, we expect analgesia of the cervix and vagina to be produced, but not sufficient to tolerate the presence of applicator rods in the body of the uterus. The block may be difficult to perform in obese patients and the failure rate is known to increase with age.[7] Classical sacral anomalies are well described and have been confirmed recently by magnetic resonance imaging.[5] Finally, the block may well be of insufficient duration (which may be due to the dose of bupivacaine used), despite the majority of analgesic demand occurring in the first 4 h of treatment.

Lumbar epidural block

This would seem ideally suited to the treatment of pain produced by LDR therapy. A low concentration local anaesthetic/opioid infusion, as is popular in many obstetric units, should provide excellent postoperative analgesia and could be topped up for applicator removal at the end of treatment. The use of such a technique has been described, albeit indirectly, in a recent study.[11] Twenty pelvic brachytherapy patients were given epidural anaesthesia for applicator insertion, followed by postoperative infusion of 0.125% bupivacaine with fentanyl 3 $\mu g\ ml^{-1}$. Patients were only assessed twice daily for block height and motor weakness. Although precise details were not given, all patients received adequate pain relief with minimal systemic opioids. The otherwise infrequent mention of epidural use in the literature,[10 16 20] may support our concerns over its safety for high risk cases in an isolated setting with limited supervision and monitoring.

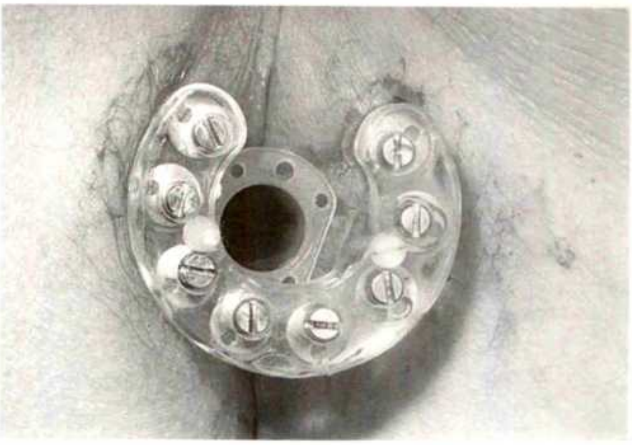

Fig 3 Plastic template stitched to peri-anal skin holding eight hollow afterloading needles containing iridium wire.

Interstitial brachytherapy for anal, low rectal, vaginal, vulval and penile cancers

Anal and low rectal cancers

In the last decade, it has been clearly shown that anal cancer can be treated at least as well by radiotherapy as by the much more radical treatment of abdomino-perineal resection. Squamous carcinomas up to 5 cm have a 3-yr survival of 93% following radiotherapy.[35] Surgery is the treatment of choice for adenocarcinomas of the low rectum impinging on the anus. However, radiotherapy can treat tumours extending to 8 cm beyond the anal margin. The 3-yr survival in patients who either refused surgery, or were judged inoperable on technical or medical grounds, was 57%.[35]

The technique involves implantation of up to eight hollow stainless steel needles, of up to 10 cm in length, around the anal canal. They are secured in a horse-shoe shaped, rigid plastic template to ensure near perfect geometrical distribution of radiation dose (Figs 3 and 4). Iridium wire is cut to size and inserted into the needles 1–2 h after the implant has been sited under anaesthesia.

Vaginal and vulval cancers

Vaginal cancer is becoming more common, often following successful treatment of cervical lesions. Tumours in the lower and middle thirds of the vagina can be treated in a similar fashion to anal cancer. The vulva tolerates radiation poorly, but localized iridium needles implanted for up to 7 days are useful for incompletely excised or inoperable tumours.

Penile cancer

The use of radiotherapy can avoid amputation of the penis for tumours of up to 4 cm. External beam radiotherapy provides an 80% cure rate,[27] but many patients develop

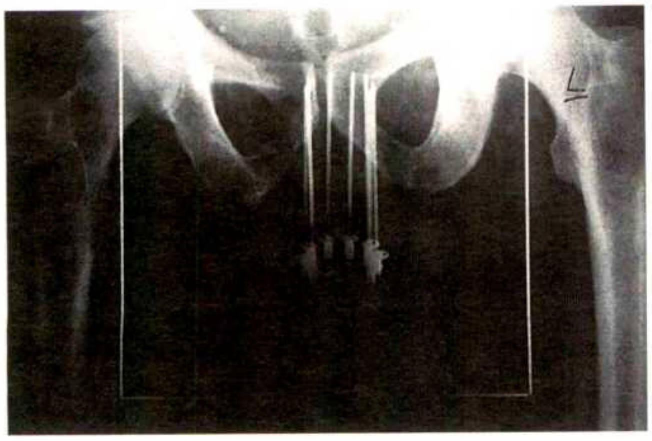

Fig 4 A-P radiograph of palisade of hollow afterloading needles surrounding the anus and lower rectum.

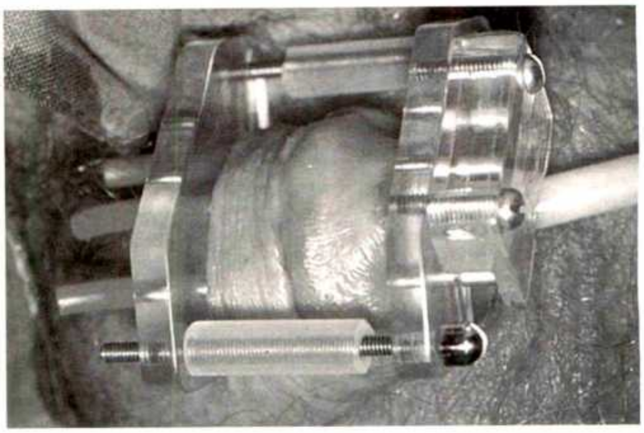

Fig 5 Afterloading template iridium implant for carcinoma of penis.

complications such as fibrosis of the penile shaft, erectile dysfunction and urethral strictures. However, implanting the tumour-bearing area with iridium reduces the incidence of complications[19] (Fig. 5).

Analgesia for interstitial brachytherapy

General or regional anaesthesia is required to site pelvic interstitial implants. Postoperative analgesia is greatly enhanced by appropriate selection of the following techniques.

Caudal epidural block

This provides excellent postoperative analgesia for patients having anal, vaginal, vulval or penile implants. The pudendal nerve (S2–4) supplies the perineum and pelvic floor through the inferior haemorrhoidal and perineal branches, and the penis or clitoris through their corresponding dorsal nerve branches. However, the pudendal nerve is not the only sensory nerve to the perineum. The labia majora, base of penis and the scrotum receive mixed sensory innervation from the terminal branches of the ilioinguinal (L1) and genitofemoral (L1–2) nerves. The injection of 0.375% bupivacaine 20 ml through the sacral hiatus, would be expected to provide a sensory block to a maximum height of L1.[25] More commonly, the block only reaches the lower lumbar roots, resulting in inadequate analgesia in a small number of patients whose tumour extends outwith the distribution of the pudendal nerve.

Spinal 'saddle' block

Spinal 'saddle' block with 0.5% hyperbaric bupivacaine 1.0 ml in the sitting position, is a useful alternative to caudal block when the sacral hiatus cannot be identified or the area of overlying skin is highly inflamed following recent external beam radiotherapy.

Penile nerve block

This is highly suitable for operations on the shaft, glans and foreskin of the penis. Since the penile urethra is supplied throughout its length by the perineal branch of the pudendal nerve, block of the dorsal nerve of the penis does not provide anaesthesia for catheterization or surgery for tumour involving the urethra. The dorsal nerve is easily blocked with 0.5% bupivacaine 20 ml at the route of the penis, as it emerges through the perineal membrane below the lower border of the pubic symphysis. Several techniques have been described, including medial or bilateral injections at the penile root, with an average block duration of 10 h.[33] Continuous dorsal nerve anaesthesia has also been described.[9]

Local anaesthetic infiltration

Patients with low rectal adenocarcinomas undergoing intraluminal irradiation do not need any form of analgesia and the treatment is performed in the outpatient department. If an iridium implant is used to give a booster dose to the tumour bed, then local anaesthetic infiltration is required.[28]

Sedation

External beam radiation in the palliation of rectal cancer can be combined with laser therapy, to control local symptoms by debulking the intraluminal growth. Photocoagulation of the lesion is painful and patients require sedation with opioids and benzodiazepines.[2]

Pre-emptive analgesia

The use of local anaesthetic blocks for interstitial brachytherapy in our unit has produced some interesting findings. Postoperative pain in anal cancer treatment can be markedly reduced for up to 2–3 days after implant insertion, by a single caudal injection. Analgesia lasting far beyond the expected duration of the block is also seen in patients with penile cancer who, following dorsal nerve block, have required no analgesia for the entire 7 days of implant insertion. This contrasts greatly with patients not receiving local anaesthesia, who seldom achieve adequate pain relief despite repeated systemic opioids.

The precise mechanisms involved in these observations are unclear. Decreased activation of nociceptive afferents may occur if the insertion of interstitial needles releases fewer inflammatory mediators (e.g. prostaglandins, bradykinin, histamine) than a standard skin incision with subsequent suturing and wound tension. The reduced peripheral sensitization of nociceptive nerve endings would lessen any degree of primary hyperalgesia. Penile, vulval and anal implants receive few C-fibre autonomic afferents and the somatic afferents are effectively blocked by local anaesthetic techniques. This may be sufficient to prevent central sensitization in the spinal cord and avoid the development of secondary hyperalgesia during implant insertion. In more major surgery, however, the clinical trials investigating pre-emptive analgesia have been disappointing because the analgesic regimen are perhaps not profound or prolonged enough to prevent central sensitization in the spinal cord.[6]

Summary

Pelvic brachytherapy presents the anaesthetist with numerous challenges. Patients vary from highly distressed young adults, to the elderly with coincidental disease severe enough to preclude surgery. The painful radioactive implants remain in place for a number of days. Treatment in isolated rooms reduces radiation exposure to staff, but makes close postoperative monitoring difficult, so the analgesic technique should involve minimum risk to the patient. Although there is very little published evidence of specific analgesic techniques in this area, knowledge of these problems allows the anaesthetist to select appropriate systemic analgesics and regional blocks to provide safe and effective pain relief.

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BJA

SHORT COMMUNICATIONS

Effects of temperature and haematocrit on the relationships between blood flow velocity and blood flow in a vessel of fixed diameter

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Background. To determine whether temperature and haematocrit (Hct) alter the relationship between blood flow (BF) and blood flow velocity (BFV).

Methods. Using a transcranial Doppler apparatus, we measured the peak velocity of whole blood cells pumped by a cardiopulmonary bypass (CPB) circuit, through a 0.15-cm internal diameter segment of rigid tubing. BF and BFV relationships were obtained at temperatures of 19, 28, and 37°C and at Hct of 0.05, 0.22, 0.39, and 0.54, by altering CPB flow over a range from 10 to 100 cc/min. Linear regression analysis was performed.

Results. The relationship between velocity and flow for the pooled Hct data was $y=(0.43)x+0.86$, $r^2=0.998$ and 95% CI (0.999–1) whereas the association for the temperature data was $y=(0.42)x+0.02$, $r^2=0.9998$ and 95% CI (0.999–0.9997). Changes of blood viscosity had no effect on velocity at a given flow rate. The combined effect of Hct and temperature on velocity for the relationship with flow is expressed by: $y=1.3+2.4x$.

Conclusion. In fixed diameter vessels with laminar flow, the linear relationship between flow and velocity is not affected by changes in temperature and Hct in clinical ranges. These results are explained by the Fahraeus–Lindquist effect. They support the use of transcranial Doppler sonography to estimate cerebral blood flow in infants who may have large variations of Hct and/or temperature during bypass.

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Keywords: anaesthesia, paediatric; equipment: transcranial Doppler apparatus; blood, haemodilution; complications, hypothermia

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Transcranial Doppler sonography (TCD) is used to measure cerebral perfusion. It is non-invasive, has a high temporal resolution, and allows continuous monitoring. The major limitation is that it measures blood flow velocity (BFV) rather than blood flow (BF). Clinical and animal studies have found a good correlation between changes in BFV in the basal cerebral arteries and BF during physiological changes such as Pa_{CO_2} and temperature.[1] Blood temperature and haematocrit (Hct) can influence blood viscosity,[2] and might change the relationship between BF and BFV. This study was designed to determine whether temperature and Hct alter BFV, in a model, simulating a small basal cerebral artery in infants.

Methods and results

A cardiopulmonary bypass (CPB) circuit primed with human whole blood was connected to a 0.15-cm internal diameter segment of rigid tubing. The CPB flow rates were adjusted between 10 and 100 cc min^{-1} with increments of 10 cc min^{-1}. Calibration of this system was by timed collection of all effluent blood from the circuit into a graduated

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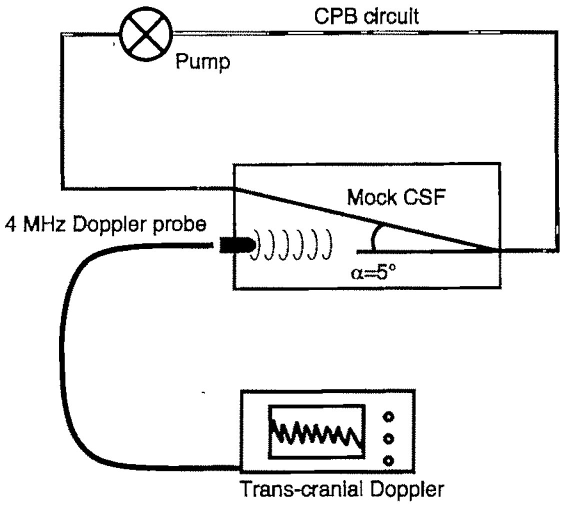

Fig 1 Experimental system used.

cylinder. Peak velocity through this tubing was determined by TCD using a 4 MHz continuous wave Doppler probe (Medasonics, Fremont, CA, USA). This segment of tubing passed through a glass box containing mock cerebrospinal fluid. The TCD probe was fastened to the box through a hole created on the box side, which was subsequently sealed with epoxy glue (Fig. 1). The TCD probe was 30 mm distant from the tube, allowing for blood velocity recordings. The angle of insonation was set at 5°. Flow-velocity data were obtained at temperatures of 19, 28 and 37°C using outdated human packed red blood cells (PRBC) reconstituted with outdated plasma to give a Hct of 0.39. The velocity was also recorded at Hct of 0.05, 0.22, 0.39, and 0.54 using reconstituted whole blood at a temperature of 37°C. Five velocity values were recorded at each interval and averaged. Linear regression analysis and the coefficient of correlation (r^2) were performed and calculated using GraphPad InStat version 3.00 for Windows 95 (GraphPad Software, San Diego, CA, USA). $P<0.05$ was considered statistically significant.

There was a strong linear relationship between blood flow and blood velocity at each set of conditions ($r^2>0.99$). The velocity varied directly with flows at all Hct (Fig. 2). The relationship between flow and velocity for the pooled Hct data was $y=(0.43)x+0.86$, $r^2=0.998$ and 95% CI (0.999–1). Similarly, temperatures from 19 to 37°C did not affect the relationships between flow and velocity ($y=(0.42)x+0.02$, $r^2=0.9998$ and 95% CI (0.999–0.9997)). The combined effect of temperature and Hct changes on velocity was y (BFV)=1.3+2.4x (BF).

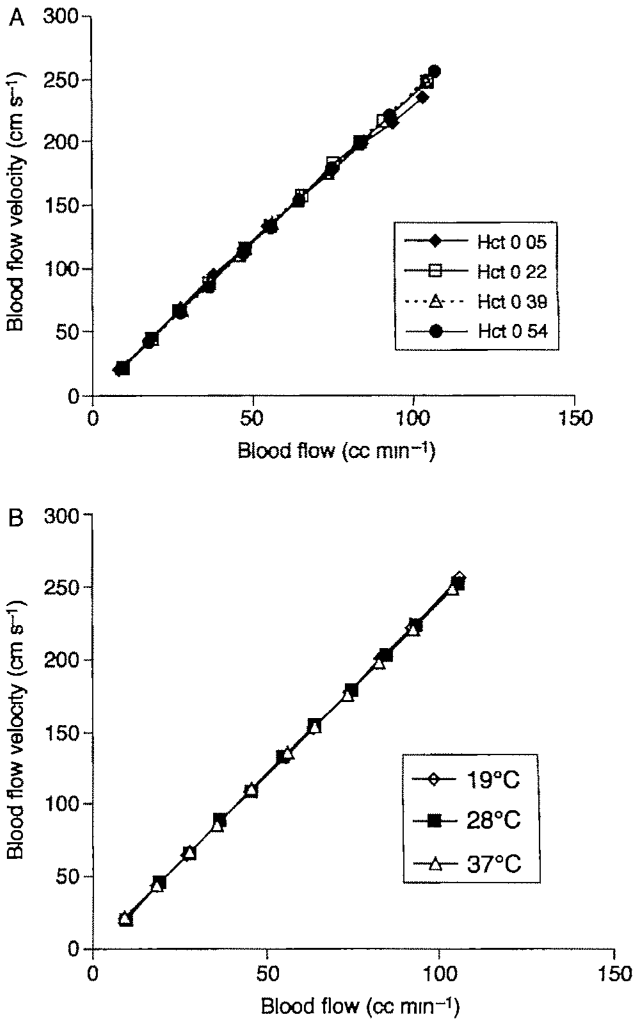

Fig 2 (A) Effect of Hct changes on blood velocity. (B) Effect of temperature variations on blood flow velocity

Comments

We found a linear relationship between blood flow and peak blood flow velocity, in fixed diameter vessels with laminar flow. This relationship is not altered by changes in temperature and haematocrit within clinical ranges. Variations of blood viscosity which are affected by Hct and temperature do not affect the peak velocity in a small fixed diameter vessel, as peak velocity for a given flow rate was similar whatever the temperature or Hct.

In experimental and clinical settings, many physiologic factors affect cerebral blood flow velocity. Among them, Hct and core temperature have been widely studied. In adults, normovolaemic haemodilution with a decrease of Hct from 38 to 30% was associated with an average 16% increase in cerebral blood flow velocity.[3] In children, an inverse relationship between cerebral blood flow velocity and Hct has been demonstrated during deep hypothermic cardiopulmonary bypass.[4] During deep hypothermia, cerebral blood flow was reduced by 40%.[5] The cerebral blood flow velocity was also correlated with cerebral blood flow. In eight children undergoing cardiac surgery with deep hypothermia, the authors demonstrated that cerebral blood flow velocity was reduced to 33% of the control value, whereas oxygen consumption was decreased to 20% of control.[1]

The effects of Hct and temperature on cerebral blood flow velocity can be related either to their effect on blood viscosity, on cerebral blood flow adaptation to cerebral metabolic rate for oxygen, or both. Changes in Hct can change blood viscosity. Moderate haemodilution (Hct 22%) decreases blood viscosity by 30–50% at a low blood temperature[2] whereas an increase in Hct increased blood viscosity and decreased CBF.[6] Blood viscosity increases when blood temperature decreases; however, the increase in viscosity is observed mostly at temperature below 15°C.[2] The cerebral blood flow adapts with metabolic demand. It is reduced during hypothermia when oxygen consumption is decreased.[1] During polycythaemia, there is an increase in arterial oxygen content and a decrease in cerebral blood flow velocity.[6] In animals, a nitroprusside infusion administered to normalize the arterial oxygen content in polycythaemia allowed cerebral blood flow velocity to return to baseline values.[6]

In cerebral resistance blood vessels, the pressure-flow relationships are given by Poiseuille's law (equation 1):

$$Q = \pi P r^4/8l\eta \qquad (1)$$

where Q is blood flow, P is the pressure gradient across the vessel, r is the vessel radius, η is blood viscosity and l is the vessel length. Given that cerebral blood flow velocity (CBFV) is expressed by equation 2

$$\mathrm{CBFV}=Q/\pi r^2 \qquad (2)$$

We can replace Q in equation 2 to obtain equation 3

$$\mathrm{CBFV}=Pr^2/8l\eta \qquad (3)$$

In this equation, if P, r^2 and the vessel length are constant, cerebral blood flow velocity is inversely proportional to viscosity. In animals a decrease in Hct was associated with only a small 4.4% change in basilar artery diameter,[7] whereas the pial arterioles constricted as Hct decreased.[8] These results are consistent with the finding that the hyperaemia accompanying haemodilution is the result of a decrease in blood viscosity and/or an adaptive phenomenon to variations in cerebral metabolism.[7,9]

As tube length, vessel radius, and pressure are maintained constant, one would expect cerebral blood flow velocity, at a given flow, to vary proportionally with blood viscosity. In the present study, the blood flow velocity varied directly with blood flow, independently of Hct and temperature, hence independently of viscosity. Several general properties about biomechanics of blood explain these observations. The Fahraeus–Lindquist effect confirms that the apparent viscosity of whole blood varies with the Hct. Normally, plasma viscosity is 1.2–1.3 times that of water, whereas the blood viscosity is 2.4 times that of plasma. Furthermore, the effect of viscosity of whole blood depends critically on the size of the vessel through which it flows. When blood is flowing through vessels narrower than 2 mm in internal diameter, the apparent viscosity tends toward that of plasma.[10] This explains the present observation and confirms that, in a 1.5-mm internal diameter tube intended to simulate the diameter of an infant's mean cerebral artery, viscosity does not affect blood flow velocity recordings.

In conclusion, we found that in a small vessel of fixed diameter, wide variations of temperature, Hct and viscosity did not affect the relationships between blood flow velocity and blood flow. It supports the clinical usefulness of TCD to assess cerebral blood flow in infants who have large changes of Hct or temperature which can occur during cardiopulmonary bypass.

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Improvement of information gained from the pre-anaesthetic visit through a quality-assurance programme[†]

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Background. Pre-anaesthetic evaluation is a fundamental component of anaesthetic practice. The aims of the present study were to assess the quality of the preoperative anaesthetic information gathered and to observe the quality profile after the introduction of a standardized form. This occurred through a four-step quality assurance programme over a 4-yr period.

Methods. The proportion of cases in which a complete recording of data was collected at the preoperative assessment was evaluated by searching in each patient's medical record for what was considered to be the minimum information required to provide satisfactory perioperative care. Fifteen criteria were selected. The recovery profile for each indicator and a global quality index (GQI expressed in %) for each patient's record were collected. In phase 1, the existing situation was assessed. Next, a standardized pre-anaesthetic form (PAF 1) was designed and its implementation evaluated (Phase 2). Phase 3 was performed 16 months after implementation of PAF 1 to assess the long-term value. The form was revised (PAF 2) and its use evaluated again 6 months later (Phase 4). For each evaluation, the records of a 1-month period were examined. Overall 1129 medical records were audited.

Results. The GQI increased significantly from 62 to 88% with similar changes for both elective and emergency cases. The recovery profile was improved for most indicators.

Conclusions. We conclude that the quality of information recorded from the pre-anaesthetic visit is improved by using a standardized form. This will hopefully help to improve patient outcome and facilitate computerization of the anaesthetic record.

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Keywords: anaesthesia; risk, management; surgery, preoperative period; anaesthesia, audit; records, medical

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Surgical mortality and morbidity are not only the consequences of the surgical procedure itself, but also of the patient's preoperative physical status.[1–4] The preoperative anaesthetic visit is aimed primarily at detecting these medical conditions and assessing their severity. Subsequent preoperative optimization of the patient's condition reduces perioperative and anaesthesia-related risks.[5 6] The preoperative anaesthetic visit also serves to guide the most appropriate anaesthetic technique and to provide patient information. This visit is thus a fundamental step of the surgical process[7 8] and this has been recognized in France by a law enacted in 1994 that makes the preoperative visit mandatory before every anaesthetic administration,[9] at least 2 days before surgery for non-emergency procedures.[9]

Despite the recognized medical and financial importance of this visit,[8] there are neither detailed guidelines, nor any definition of what is the minimum/necessary information required. Most anaesthesia departments, aware of the importance of this information, have created their own preoperative assessment forms in order to standardize the information recorded. The usefulness and effectiveness of this strategy have, however, never been assessed. The only available literature relates to the pre-anaesthetic questionnaire.[10] The aims of the present study are to assess the proportion of complete recording of data collected at the

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[†]Presented in part at the annual meeting of the French Society of Anaesthesia and Intensive Care in September 2000

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Table 1 Criteria incorporated in the global quality index (GQI). A: criteria used during the first three phases of the quality assurance programme. B criteria added in the fourth phase ASA=American Society of Anesthesiologists, ICU=intensive care unit, NSAIDs=non-steroidal anti-inflammatory drugs

A **Phases 1–3**	B **Phase 4**
1 Date of pre-anaesthetic visit	16. Tolerance to physical stress and presence of sputum
2 Name of anaesthesiologist performing pre-anaesthetic visit	17 Recent weight loss (kg)
3. Allergy	18 Clinical conclusion
4. Patient's weight (kg)	19. Contra-indication to NSAIDs
5 Ambulatory surgery	20 Pre-anaesthetic review immediately before surgery
6. Heart rate	21 Information on postoperative analgesia
7. Arterial blood pressure	22. Information on ambulatory surgery
8. Cardiovascular examination	23 Information on blood transfusion
9. Respiratory examination	24 Information on transfer to ICU
10 ASA score	25 Immunosuppression and/or nosocomial status
11. Type of anaesthesia accepted by the patient	
12 Risk of aspiration	
13. Type of postoperative analgesia	
14. Postoperative transfer to ICU planned	
15 Difficult intubation criteria	

preoperative assessment and to observe the quality profile after the introduction of a standardized form through a four-step quality assurance programme over a 4-yr period.

Methods and results

Description of the process

This programme was started in November 1995, in a university teaching hospital in the suburbs of Paris (France) where the pre-anaesthetic visit and the anaesthetic itself are usually not provided by the same doctor.

The first step was to assess the existing situation. At that time pre-anaesthetic information was written on the reverse side of the anaesthesia record sheet. The quality of the pre-anaesthetic information was evaluated by searching each anaesthetic medical record for what was considered to be the minimum information required to provide satisfactory perioperative care. Fifteen criteria were selected after a detailed analysis of the anaesthetic literature. These criteria were those which appear repeatedly in the literature associated with an increased perioperative risk/odds ratio >2 (Table 1A) among general surgery patients. Every pre-anaesthetic assessment related to an anaesthetic procedure performed in January 1995 was retrospectively assessed (phase 1).

The second step (phase 2) began by designing a specific pre-anaesthetic assesment form (PAF 1) which was introduced after approval in a staff meeting. This form contained not only the 15 predefined criteria but also several others which were judged useful by the anaesthetic team. The anaesthetic records of November 1995 (i.e. 1 month after implementation of PAF 1) were retrospectively reviewed. The results of this second assessment were communicated to the medical team during a staff meeting and although results did not show a 100% improvement, the majority of the medical team believed that it was too early to propose any change in PAF 1.

A third assessment (phase 3) was thus performed on the files of January 1997 (i.e. 16 months after implementation of PAF 1) to assess the long-term profile. Again results of this survey were communicated to the medical team and it was decided to modify the form to improve the readability and to include additional information. Ten new criteria were added because the medical literature published since the beginning of the programme had demonstrated new clinically relevant criteria, and also because recent French legal obligations regarding patient information required us to modify our practice (Table 1B). The pre-anaesthetic assessment form version 2 (PAF 2) also asked for more detailed descriptions of previously used criteria.

Phase 4 consisted of an assessment of all anaesthesia records of March 1999 (i.e. 6 months after implementation of PAF 2). The new criteria defined in phase 4 were recorded but could not be compared to previous data.

Data recordings and statistical analysis

Fourteen of the 15 first quality criteria were recorded as 'yes' or 'no' while risk factors for difficult intubation were quoted as a percentage (four factors were required on PAF 1 and six criteria on PAF 2).

For each PAF, a global quality index (GQI) was calculated with the following formula:

$$GQI=100\times(a-b)/a$$

where a is the total number of criteria selected (i.e. a=15) and b is the number of criteria lacking. Comparisons between the four steps were made using chi-square analysis or non parametric tests (Mann–Whitney U test or Kruskall–Wallis test as appropriate). Statistical significance was set at a P value less than 0.05.

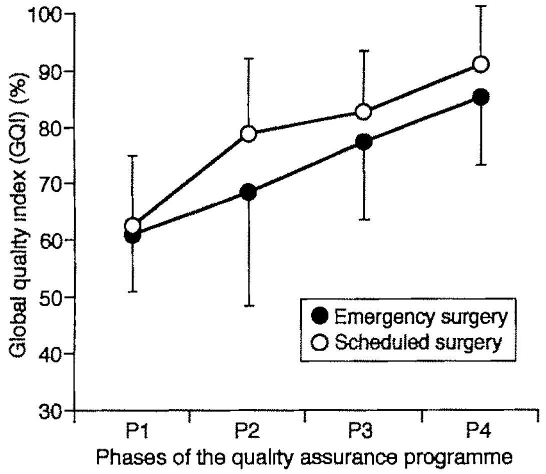

Fig 1 Global quality index (GQI) profile during the four phases

Results

Overall, 1129 anaesthetics were performed. Nine hundred and sixty-four patients' clinical records could be found (85%) and reviewed. The surgical case mix was similar in all four phases. Emergency surgery was significantly less frequent in phase 1. The GQI observed for the whole population studied, including both elective and emergency cases increased significantly during the study (Figure 1). The recovery profile was modified by the programme for each indicator.

Comment

The main finding of this study is that the quality of information recorded from the pre-anaesthetic visit is improved by using a standardized form. Indeed, human beings are consistently unable to perform repeatedly the same complex task without forgetting to collect one or several points of information. For example, in our institution, before the start of the programme, even well-trained anaesthesiologists did not record arterial blood pressure in 24% of cases and any risk factors for difficult intubation were not recorded in 6.8% of cases. This occurred despite the fact that they were aware that these questions were fundamental parts of their pre-anaesthetic assessments. Thus, even when the theoretical usefulness is accepted, the practical application is often imperfect[8] and this is a main goal of quality-assurance programmes.

This study had two weaknesses. First, it does not answer the question as to whether improving the quality of the pre-anaesthetic assessment improves patients outcome or perioperative care. However, it has been shown by the Australian Incident Monitoring Study that inadequate preoperative assessment and management were associated with a six fold increase in mortality.[7] The three most common contributing factors were inadequate airway assessment, imperfect patient data transmission, and inadequate patient evaluation. Moreover, deficiencies in written notes in medical records were the most common breakdown in patients' data communication.[7] The second weakness is that analysis of medical records was made retrospectively. However, we assessed written information (i.e. the only objective knowledge that the attending anaesthesiologist could find at the arrival of the patient in the operating room). Moreover, the criteria to be assessed had been determined before looking at the medical records.

The overall quality index increased from 62 to 88% during the four phases of the programme. Almost every indicator was better recorded and none was worse in phase 4 compared to phase 1. We believe that two main factors should be discussed when assessing the profile of this change. First, a learning curve effect induced a transient decline in recording several indicators. It is interesting to note that this transient negative effect was seen only for indicators which were well recorded in the absence of a specific form and for which the margin of improvement was small. Conversely, indicators which were frequently not documented before the programme showed an immediate and sustained improvement. Second, the design of the form and its practical presentation also played a significant role, particularly for those indicators which were given more space on the form (open questions) or were asked by a specific question. By contrast, reduction of the space on the form for recording the date of the pre-anaesthetic assessment visit resulted in a decrease in the percentage of forms with a recorded date.

In conclusion, this programme resulted in a marked improvement in the proportion of complete recording of data collected at the preoperative assessment. Given the conclusions of previous reports,[7] this suggests that such a programme may lead to improvement in patient outcome, though this was not evaluated in this study.

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How reliable is length-based determination of body weight and tracheal tube size in the paediatric age group? The Broselow tape reconsidered

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Background. The Broselow tape was designed to estimate body weight and tracheal tube size on the basis of the body length of emergency paediatric patients. The tape was validated previously in US populations. We assessed its accuracy in a sample of European children by reviewing paediatric anaesthetic charts at the Triemli City Hospital for 1999.

Methods. Age, body length and body weight measured before surgery as well as the size of the tracheal tube used were recorded. The body weight was estimated on the basis of body length using the Broselow tape and was compared with the measured weight. Tracheal tube size selections using the Broselow tape and an age-based formula were compared with the size of the tube used.

Results. A good correlation was found between the Broselow weight and the measured weight (r^2=0.88) Bland–Altman analysis revealed a mean bias of –0.52 kg for the entire study population. For children ≤20 kg the mean bias was –0.05 kg, and for children >20 kg was –1.05 kg. The Broselow weight was found to be within a 10% error of the measured weight in 65% of children. Tracheal tube selection by the Broselow tape method was adequate in 55% but underestimated the actual tube size in 39%. The age-based formula matched the actual tracheal tube size in 41% of children but overestimated it in 57%.

Conclusions. The Broselow tape is an accurate means to assess body weight from length in smaller children; in older children it underestimated body weight. Endotracheal tube size selection by the Broselow tape appears to match the size of the tube used better than the age-based formula. The results in a European sample of children are comparable to the US data

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The Broselow tape was designed to estimate body weight and drug dosage, as well as endotracheal tube size, of emergency paediatric patients on the basis of body length. The tape is recommended by the Advanced Trauma Life Support®[1] and the Pediatric Advanced Life Support[2] courses which have grown in popularity all over Europe in recent years. Validation of the Broselow tape was done for weight[3] and for endotracheal tube size selection[4,5] in children from the United States. The aim of this study was to assess the accuracy of the Broselow tape in European children.

Methods and results

All 904 paediatric anaesthetic charts at the Triemli City Hospital from 1999 were reviewed and the following information was recorded: age (yr), gender (m/f), ASA classification, body length (cm), body weight (kg) and the size (internal diameter [ID] in cm) of the uncuffed tracheal tube size used. On admission to the paediatric ward, body weight and body length were measured to the nearest 0.1 kg and 0.1 cm, respectively. Charts from 222 children (24.6%) who had a body length exceeding the range of the Broselow tape (up to 154 cm) and 97 charts (10.7%) in which data were estimated or incomplete were excluded from statistical analysis. The remaining 585 charts of 330 male (56.4%) and 255 female children (43.6%) were used for statistical analysis by Statview 5.01® software (SAS Institute Inc., Cary, USA). A P value <0.05 was considered statistically significant. All statistical analyses were performed separately for children weighing ≤20 kg and those weighing >20 kg. Children were either ASA I or II. They ranged in age from 6 months to 11 yr 10 months. Forty-eight per cent of the children were aged between 2 and 6 yr; 13% were younger than 2 yr. Body weight ranged from 3.5 kg to 39.3 kg; 45% of the children weighed between 10 and 20 kg.

Length-based weight determination

The body weight was estimated using the Broselow tape (Broselow weight) on the basis of the body length measured before surgery, and was compared with the measured body weight. Using a Bland–Altman plot (Fig. 1) to determine the mean bias and the limits of agreement.[6,7] There was a statistically significant mean bias of –0.52 kg (P<0.0001) and the limits of agreement were –5.8 kg and 4.8 kg (Fig. 1). The mean bias for children ≤20 kg was –0.05 kg (limits of agreement: –3.0/2.9 kg) and for children >20 kg was –1.05 kg (limits of agreement: –8.0/5.9 kg).

The Broselow weight was found to be within a 10% error for 65%, and a 15% error for 83% of the children. The 10% error for children ≤20 kg was 66% and for children >20 kg was 65%. Differences between these groups were pronounced above the 15% error range (≤20 kg: 14%; >20 kg: 19%). There was a good correlation between Broselow weight and measured weight (r^2=0.88), with no significant differences between female and male children (P=0.28; Student's t test). For children ≤20 kg, r^2 was 0.9 and for children >20 kg; r^2 was 0.58.

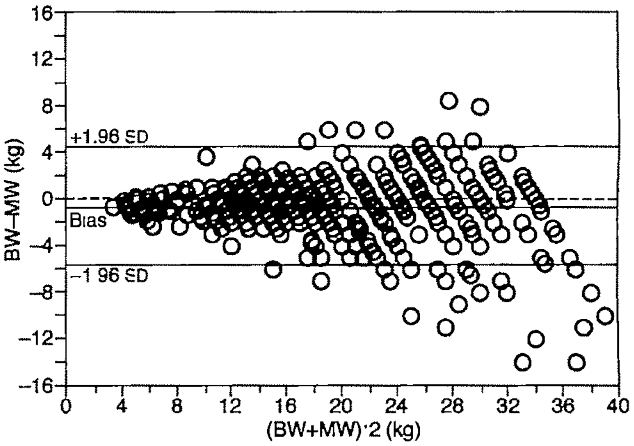

Fig 1 Bland–Altman analysis for body weight determined by the Broselow tape. BW, Broselow weight in kg (weight determined by the Broselow tape); MW, measured body weight in kg. Mean bias was –0.52 kg (95% confidence intervals [CI]· –0.7/–0 3 kg; lower and upper limits of agreement were –5.8 kg (CI: –6.2/–5.4 kg) and 2.6 kg (CI. 4.5/5 2 kg), respectively)

Length-based tracheal tube size selection

The tracheal tube size selection using the Broselow tape was the same as the size used in 55% of cases, and underestimated the used size in 39% of cases. Results of the two different weight groups were comparable (matching ≤20 kg: 57%; >20 kg: 53%). Tracheal tube size selection using the age-based standard formula ([age in years+16]4^{-1}) matched the used size in 41% of cases, and overestimated it in 57% of cases. There was a significant difference in tracheal tube size selection between the Broselow tape method and the age-based formula (P<0.001, χ^2-test).

Comment

The Broselow tape provided accurate estimation of the body weight based on measured body length. The tape slightly underestimated the body weight of the whole study population. In smaller children with a body weight ≤20 kg, the underestimation was negligible. Underestimation of body weight was pronounced in children with a body weight >20 kg.

The tracheal tube size selection by the Broselow tape met clinical needs better than estimation using a standard age-based formula. Correct match was more frequent using the tape than the formula. Moreover, the observed underestimation by the tape may be less relevant clinically in terms of airway injury than the frequent overestimation that occurs when using the standard age-based formula.

The results of the current study performed in a European paediatric population are comparable to the published data in US paediatric populations for body weight estimation[3] and tracheal tube size selection.[4] However, tracheal tube size selection using the Broselow tape was not superior to the age-based formula used in one US study.[5]

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Effect of spinal anaesthesia on plasma concentrations of glutathione S-transferase

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Background. Plasma glutathione S-transferase (GST) concentration measurement is a sensitive and specific index of hepatocellular injury. GST concentration increases after anaesthesia with most volatile anaesthetic agents, but not after propofol. Such increases are thought to result from reduced liver blood flow. The effect on GST concentration of spinal (subarachnoid) anaesthesia, which might also reduce liver blood flow, is not known.

Methods. We studied the effects of spinal anaesthesia on GST concentrations measured by specific radioimmunoassay in 33 patients undergoing intermediate orthopaedic, general or gynaecological surgery. GST concentrations were measured before anaesthesia and 3, 6 and 24 h after induction of anaesthesia. Hypotension (systolic blood pressure <70% of pre-induction value) was rapidly corrected with i.v. ephedrine.

Results. Mean duration of surgery was 41 min (range 11–80). No increase in GST concentration was observed at any time, but at 24 h GST concentration was significantly reduced ($P<0.05$). One patient in whom hypotension was not treated developed a greatly increased GST concentration at 3 h.

Conclusion. We found no association between spinal anaesthesia and disturbance of hepatocellular integrity when hypotension does not occur or is rapidly corrected.

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Subclinical hepatic injury after anaesthesia continues to provoke interest, particularly with newer, more sensitive methods of assessment such as measurement of plasma glutathione S-transferase (GST) concentration. GST is rapidly released into the circulation after hepatic damage and its short plasma half-life (<90 min) allows early detection of hepatic injury and its resolution. Using such assessment, various workers have shown minor disturbances of hepatocellular integrity after anaesthesia with halothane, enflurane, sevoflurane[1] and desflurane[2] but not propofol.[1] Isoflurane anaesthesia has been shown by several workers to have no effect on plasma GST concentration[1] but this has been contested.[2] Reduced liver blood flow is believed to be responsible for the observed increases in GST concentration after anaesthesia.[3] Spinal (subarachnoid) anaesthesia may also reduce liver blood flow[4] but it is not known whether spinal anaesthesia may induce subclinical hepatic injury. We have therefore assessed the effect of spinal anaesthesia on hepatocellular integrity using a well-validated technique for measurement of plasma GST concentration.

Methods and results

After obtaining approval from the local ethics committee, written informed consent was obtained from 34 randomly selected adult patients (ASA I or II) who were to have intermediate orthopaedic, general or gynaecological surgery which was expected to last 30–120 min. Exclusion criteria included previous liver disease, general anaesthesia within the preceding 3 months, contraindications to spinal anaesthesia, alcohol intake >3 u day^{-1} and body weight >20% above ideal weight. Patients receiving medications likely to interfere with liver function were also excluded.

Premedication was with an oral benzodiazepine 1 h before surgery. Spinal anaesthesia was induced in the lateral position at the L3/4 interspace, using either 2% lidocaine, 0.5% bupivacaine or 0.5% bupivacaine in 8% dextrose ('heavy' bupivacaine) as indicated clinically. Midazolam was given intravenously for sedation if required. Patients received i.v. Ringer lactate solution 500–1000 ml during surgery. Arterial pressure was measured every 5 min throughout anaesthesia; heart rate and oxygen saturation were monitored continuously. Hypotension, defined as systolic blood pressure <70% of pre-induction value for >5 min, was corrected with i.v. ephedrine.

Blood was sampled into heparin tubes immediately before induction of anaesthesia and 3, 6 and 24 h later for measurement of plasma GST B_1 concentration (or α class GST) by specific radioimmunoassay.[5] The reference range for GST B_1 concentration is 0.5–4.8 µg litre^{-1}.

Data were analysed by Friedman's test for repeated measurements. The Wilcoxon signed rank test was used to examine changes in GST concentration from before anaesthesia to 3, 6 and 24 h after induction of anaesthesia. Analysis was performed with Minitab for Windows (version 12).

Of the 34 patients studied, one was excluded from analysis because of lost samples. Data from the remaining 33 (18 male; mean age 57 (range 22–81) yr) were analysed. This sample size gave the study a power of 78% for a change in GST concentration >0.7 µg litre^{-1}. Sixteen patients had orthopaedic surgery such as knee arthroscopy, tendon repair or fixation of lower limb fractures; 12 patients had general surgical procedures such as inguinal hernia repair or haemorrhoidectomy, and the remaining five patients had pelvic floor repair. Mean duration of surgery was 41 (range 11–80) min. Five patients received 2% lidocaine (mean 3.75 ml), 10 received 0.5% plain bupivacaine (mean 3.25 ml) and 18 received 0.5% 'heavy' bupivacaine (mean 3.04 ml). Twenty-one patients received midazolam (mean dose 4.4 (range 2–10) mg).

Median (interquartile range) GST concentrations (µg litre^{-1}) were: before anaesthesia, 2.25 (1.7, 2.9); 3 h, 2.1 (1.8, 3.4); 6 h, 2.0 (1.5, 3.85); 24 h, 1.8 (1.4, 2.95). Significant temporal changes in GST concentration occurred after anaesthesia ($P<0.05$). No increase in GST concentration was observed, but at 24 h GST concentration was significantly less than that found before anaesthesia (Fig. 1). Three patients (9%) developed GST concentrations >4.8 µg litre^{-1} during the study period; one patient had a greatly increased (more than twice the upper limit of the reference range) GST concentration at 24 h. Three patients had GST concentration >4.8 µg litre^{-1} in blood samples obtained before anaesthesia. The mean maximum (range) reduction in systolic blood pressure during spinal anaesthesia was 27 (0–57)%. Seven patients required correction of hypotension with i.v. ephedrine (total dose 6–12 mg). Two of these patients had received 2% lidocaine, one had received 0.5% plain bupivacaine and four had received 0.5% 'heavy' bupivacaine. One further patient developed hypotension (52% reduction in systolic blood pressure)

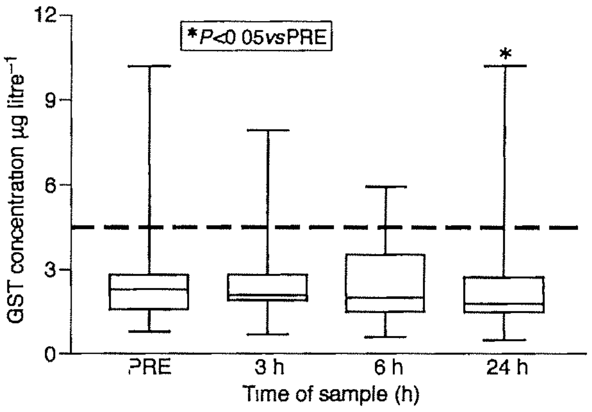

Fig 1 Box and whisper plot of plasma glutathione S-transferase (GST) concentrations (µg litre^{-1}) in 33 patients receiving spinal anaesthesia The dotted line represents the upper limit of the reference range.

which inadvertently was not corrected with ephedrine; GST concentration increased greatly at 3 h in this patient (7.2 μg litre^{-1} compared with 1.8 μg litre^{-1} before anaesthesia). Overall changes in GST concentration were not related to hypotension, type of local analgesia used for spinal anaesthesia or administration of midazolam.

Comment

We have shown that plasma GST B_1 concentration does not increase after spinal anaesthesia. In contrast, GST concentration is known to increase after anaesthesia with halothane, enflurane, sevoflurane[1] and desflurane.[2] Such increases are thought to result from a reduction in hepatic blood flow. The lack of change in GST concentration in the present study appears to agree with the known effects of spinal anaesthesia on liver blood flow. Liver blood flow is reduced in spinal anaesthesia but this is related to systemic hypotension.[4] If hypotension does not occur,[6] or if it is corrected with ephedrine,[7] liver blood flow is not reduced. Seven patients in our study developed hypotension which was rapidly corrected with administration of ephedrine. GST concentrations did not increase in these patients suggesting that liver blood flow was maintained. One further patient developed hypotension which was not corrected. The large increase in GST concentration observed at 3 h in this patient suggests that liver blood flow was significantly reduced. As hypotension did not occur in the remaining 26 patients it is unlikely that liver blood flow was adversely affected and hence why increased GST concentrations were not observed. The finding that GST concentrations at 24 h were significantly lower than before anaesthesia has been reported previously after general anaesthesia and is thought to reflect changes in hydration status.[8] A similar explanation may account for the finding of increased GST concentrations in three patients before anaesthesia.[9] The mechanism of the secondary increases in GST concentration observed at 24 h is not known. In conclusion, the findings from this study suggest that disturbance of hepatocellular function does not occur after spinal anaesthesia when hypotension does not occur or is rapidly corrected with ephedrine.

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BJA

CASE REPORTS

Submental intubation in a patient with beta-thalassaemia major undergoing elective maxillary and mandibular osteotomies

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A 33-yr-old woman with marked maxillo-facial deformities as a result of underlying beta-thalassaemia major was to undergo corrective maxillary and mandibular osteotomies. The placement of an endotracheal tube posed a problem in this patient because of anatomical deformities in her nasal passage, surgical constraints on using the oral route, and reluctance of the patient to have a tracheostomy. This case report describes the use of a submental tracheal intubation technique, and the associated anaesthetic difficulties encountered in patients with this pathology.

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Keywords: anaesthesia; equipment, tubes tracheal; intubation tracheal, submental; complications, haemoglobinopathy; complications, beta-thalassaemia major

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Thalassaemias are haematological diseases characterized by the absence or reduction in the globin chains of adult haemoglobin. Beta thalassaemia is a subset that lacks the beta chains. The excess of alpha chains causes the abnormal haemoglobin to be destroyed in the bone marrow and in the periphery. It is widespread throughout the Mediterranean, the Middle East, North Africa, the Indian subcontinent, and Southeast Asia. Inadequately treated patients develop severe anaemia, splenomegaly, bone changes, and are prone to infection. The survival of these patients is determined by the severity of iron loading in vital organs following repeated blood transfusions. Ectopic marrow expansion is another prominent feature if patients survive to adulthood. These bony abnormalities can be located in many different parts of the body and facial bone involvement is common. Patients may suffer the psychological and social stigmata of having facial deformities and there is a trend towards undertaking corrective surgery in the authors' institution. We describe the perioperative difficulties encountered with a patient of Chinese origin with beta-thalassaemia major who presented for maxillo-facial surgery.

Case report

A 33-yr-old woman with beta-thalassaemia major was to undergo elective surgery to correct her facial bone abnormalities. The patient had severe hypertrophy of the bone marrow of her maxilla, which resulted in the complete obstruction of both nasal passages (Fig. 1). Tracheal intubation *via* the nasal route was deemed to be impossible. The nature of her planned procedure, mandibular and maxillary osteostomies with intermaxillary fixation, precluded the use of an oral endotracheal tube. Both the operating surgeon and the patient were reluctant to have an elective tracheostomy. After detailed discussion with both parties, tracheal intubation was, therefore, planned using a technique reported previously: submental endotracheal intubation.[1]

The other pertinent clinical features in this case related to the patient's haemoglobinopathy. Her underlying haematological disorder had necessitated repeat blood transfusions every 6 weeks since childhood and, consequently, complications arising from iron overload were a concern. Her exercise tolerance was normal, and preoperative workup included a cardiology assessment. An echocardiogram showed normal function of both ventricles. Laboratory investigations revealed some minor abnormalities in coagulation with a prothrombin time of 16 s (11.3–13.2), active partial thromboplastin time of 38.2 s (27.6–37.6), and international normalized ratio of 1.3. Indices of iron storage status were all raised with serum iron of 41 μmol litre^{-1} (5–28), ferritin of 1600 pmol litre^{-1} (15–331), and transferrin saturation of 87% (15–45).

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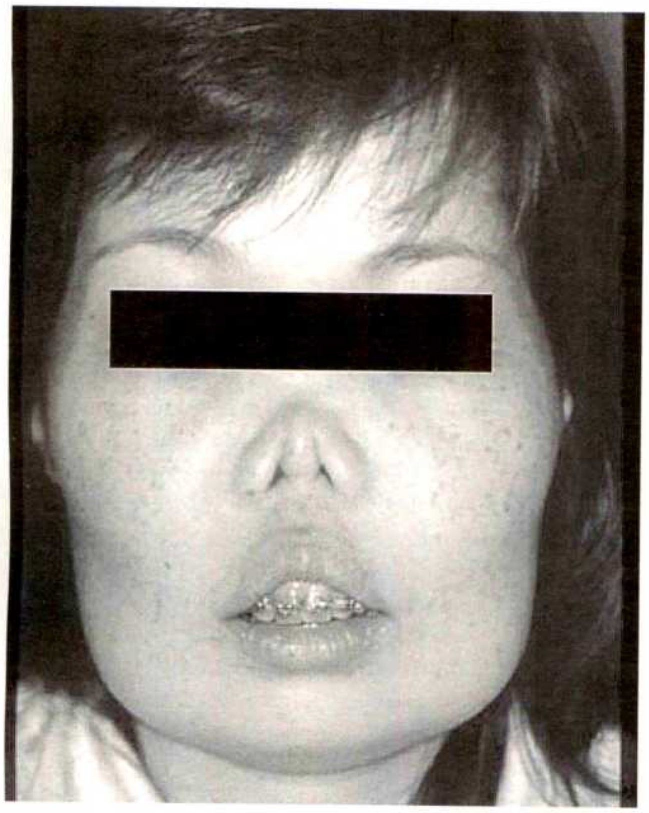

Fig. 1. Nasal intubation was virtually impossible for this patient.

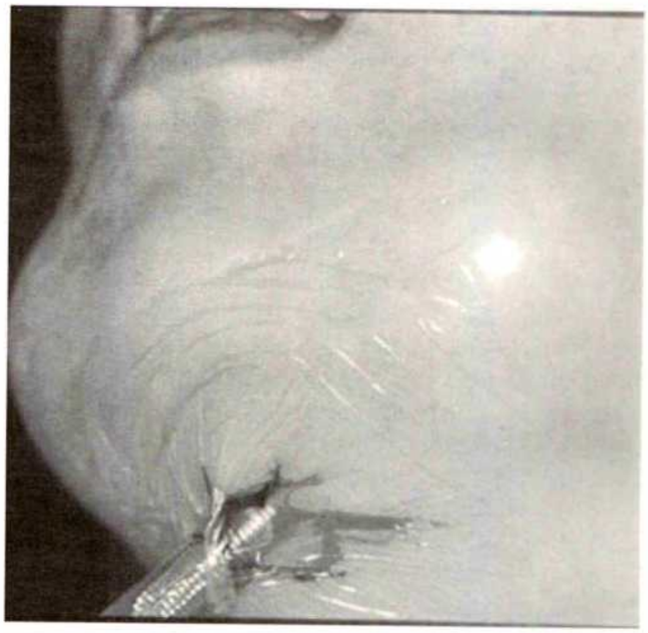

Fig. 2. Submental entry site for the endotracheal tube.

General anaesthesia was induced by i.v. injection of fentanyl 100 µg and propofol 150 mg. Direct laryngoscopy (Cormack and Lehane grade 2) and oral tracheal intubation with a size 7.0-mm ID (internal diameter) RAE™ tube (Mallinckrodt Medical, Ireland) was facilitated with injection of cisatracurium 8 mg after confirmation of easy mask ventilation. Anaesthesia was maintained by nitrous oxide in oxygen and isoflurane. A 22-G arterial cannula was inserted into the left radial artery for continuous arterial blood pressure monitoring and for ease of blood sampling. A 16-G i.v. cannula and a long central venous line (Cavafix certo 375, B. Braun Medical, Germany) were inserted into the left forearm for i.v. fluid administration and central venous pressure monitoring. Surgery commenced with a 1.5-cm incision in the left submental region. Blunt dissection, whilst identifying and preserving both submandibular and lingual nerves, was carried out until the floor of the mouth was reached. Following 3 min pre-oxygenation of the patient's lungs with 100% oxygen, a 6.5-mm ID silicone reinforced endotracheal tube (Willy Rüsch, Kernen, Germany) was inserted through the submental incision into the oral cavity. After thorough suctioning and removal of the oral tracheal tube, the reinforced tube was substituted. The process involved some degree of manipulation using a pair of Magill forceps as the new angle towards the trachea was very acute. The tube was fixed by suturing onto the submental area (Fig. 2). Surgery then preceded with Le Fort I maxillary osteotomy. To optimize surgical conditions and reduce intra-operative bleeding, the patient was positioned 15 degrees in the reverse Trendelenberg position and the systolic arterial blood pressure was maintained in the 80–90 mm Hg range. This was facilitated using aliquots of labetalol (total 15 mg).

At the stage of bone dissection and drilling, there was brisk and profuse bleeding into the surgical field, and the surgeons experienced difficulty in haemostasis. Despite vigorous fluid repletion, it was difficult to maintain a systolic arterial blood pressure of 80 mm Hg, and a central venous pressure above 0 cm H_2O. Surgery was also technically very difficult as there were minimal bony structures for plating after the osteotomy was completed and instead, a pair of hooked K wires had to be inserted into the zygomatic arches for maxillary fixation.

The estimated blood loss was 11.8 litres. The fluid repletion regimem consisted of 4 litres of crystalloid, 3 litres of colloid, 16 units of packed red cells, and 10 units each of fresh frozen plasma and platelets. Because of concern about haemostasis and ensuing blood loss, the mandibular osteostomy and intermaxillary fixation procedures were abandoned (the mandible was overgrown with bone marrow, and attempts at applying the intermaxillary fixation plate would have resulted in further brisk bleeding). As the intermaxillary fixation procedure was no longer necessary, the endotracheal tube was removed from the submental incision and substituted with a 6.5-mm ID tracheal tube through the oral route *via* direct laryngoscopy at the end of surgery. The submental incision site was then closed. Mechanical ventilation of the lungs in the intensive care unit (ICU) was continued postoperatively because of the blood loss and potential airway compromise from tissue swelling.

I.v. dexamethasone was continued postoperatively to reduce facial and laryngeal swelling. Her postoperative stay in the ICU was uneventful. She was weaned from ventilatory support and her trachea extubated 2 days after the procedure. The patient was discharged from the hospital on her tenth postoperative day.

Discussion

This method of tracheal intubation, *via* the submental route, was first described by Hernandez Altemir in 1986.[1] Since then, there have been several articles in the literature describing and modifying the technique. They were, however, mostly performed in patients following craniofacial trauma.[2 3] In these patients, nasal intubation was contraindicated because of the possibility of basal skull fracture.

We have described a unique case of a patient with severe facial bony deformities secondary to beta-thalassaemia major requiring surgery in an elective setting mainly for cosmetic reasons. Insertion of an endotracheal tube *via* the nasal passage was deemed impossible, as the maxilla was so overgrown, obstructing the nasal passages. As the planned procedure involved an intermaxillary fixation, the oral route for tracheal intubation was not feasible. A tracheostomy was considered to be an aesthetically inferior option by the patient and surgeon compared with using the submental route.

Two techniques for endotracheal tube placement *via* the submental route have been described previously. The first involved a plain oral endotracheal tube inserted after induction of general anaesthesia. A submental incision was then made and blunt dissection carried out as close to the mandible as possible until reaching the floor of the mouth was reduced. A pair of artery forceps was then passed into the channel created and the air injection port of the endotracheal tube grasped. The endotracheal tube connector was temporarily disconnected so that the body of the tube could be pulled through the floor of the mouth by the artery forceps and out through the submental opening.[4] The connector was then reattached to the rest of the breathing circuit and ventilation continued. The second technique was described in 1996 by Green and Moore[5] utilizing two separate tubes.[6] After general anaesthesia and placement of an oral endotracheal tube, a second endotracheal was introduced through a submental incision and subsequently substituted into the larynx. We chose the latter technique for two reasons. The first reason was to minimize the apnoea time while passing the endotracheal tube through the submental passage, removing and reconnecting the plastic connector. The second reason was that the silicone-reinforced tube that we used in this case has a big air injection port attached to a three-way stopcock. This is relatively large and the incision would have to have been much larger to facilitate the passage of the entire tube. However, one drawback of using this technique that has not been emphasized previously is the possibility of cuff damage. Because of the acute angle that one has to manoeuvre the tube intra-orally for tube exchange, a pair of Magill forceps has to be used for manipulation. Repeated contact between the forceps and the cuff of the tube may increase the risk of cuff damage.

Some of the anaesthetic problems associated with the thalassaemia-major syndrome have been reported previously.[7 8] Although genetic counselling has become widely available in the developed world, the authors still encounter an increasing number of patients presenting with severe forms of haemoglobinopathy, mainly from immigrant families from mainland China. Whilst modern treatments[9–11] have prolonged survival in these patients, a proportion now present for corrective surgery of facial deformities.

The massive blood loss in this case arose because of the nature of the procedure, rather than pre-existing coagulopathy. The operation involved an osteotomy impinging on overgrown bone marrow, and in retrospect, we should have anticipated the propensity for severe bleeding. It could be argued that elective cosmetic surgery may not have been prudent in this patient. However, as the demand for surgery from the patient was so overwhelming, and considering the psychosocial impact of her facial deformities, we agreed to proceed after discussing all the risks with the patient.

In conclusion, the submental method is a novel, but under utilized, technique for tracheal intubation and has only previously been described in patients with craniofacial trauma. We have described successful use in a patient with severe facial deformities, as a result of underlying thalassaemia major. We conclude that this technique is a useful option, and should not only be limited to trauma patients, but extended to a wide spectrum of patients and may avoid some of the problems inherent with a tracheostomy. Patients with beta-thalassaemia major can present with minimal symptoms but can have major intra-operative problems, especially if the operation involves correction to the bony structure. It may be reasonable to consider the use of intra-operative blood salvage techniques or means to rapidly replete intra-vascular volume.

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Management of life-threatening haemoptysis

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Massive haemoptysis represents a major medical emergency that is associated with a high mortality. Here we present two cases of life-threatening haemoptysis, the first caused by rupture of an aortic aneurysm into the lung in a 37-yr-old woman with polyarteritis nodosa and the second caused by massive bleeding from an angiectatic vascular malformation in the right main bronchus in a 21-yr-old woman. Fibreoptic bronchoscopy played an essential role in the diagnostic process and management of the respiratory tract. Diagnosis in the first case was obtained by CT scan and the aneurysm was treated surgically. In the second case, bronchial arteriography contributed to both definitive diagnosis and treatment. Initial cardiorespiratory management, diagnostic procedures and definitive therapy are described and reviewed. Adequate early management of the cardiorespiratory system is essential to the outcome. Aggressive measures to elucidate the cause of haemoptysis and prompt therapy are warranted because of the high risk of recurrence.

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Massive haemoptysis represents one of the most challenging conditions encountered in critical care. It is reported to carry 30–85% mortality in non-trauma patients.[1–5] Experience in the management of these cases is limited in Western countries because of the control of tuberculosis and infective respiratory disease. However, when encountered, adequate early management of the cardiorespiratory system is essential to the outcome. Moreover, aggressive measures to elucidate the cause of haemoptysis, together with prompt therapy, are warranted because of a high risk of recurrent lethal bleeding. Here we present two cases of massive haemoptysis, which illustrate some essential issues in the management of this condition, and review the literature.

Case reports

Patient 1

A 37-yr-old woman was admitted to a neighbouring hospital with massive haemoptysis. She had a long history of polyarteritis nodosa. During the 3 months before the admission she suffered from frequent episodes of coughing.

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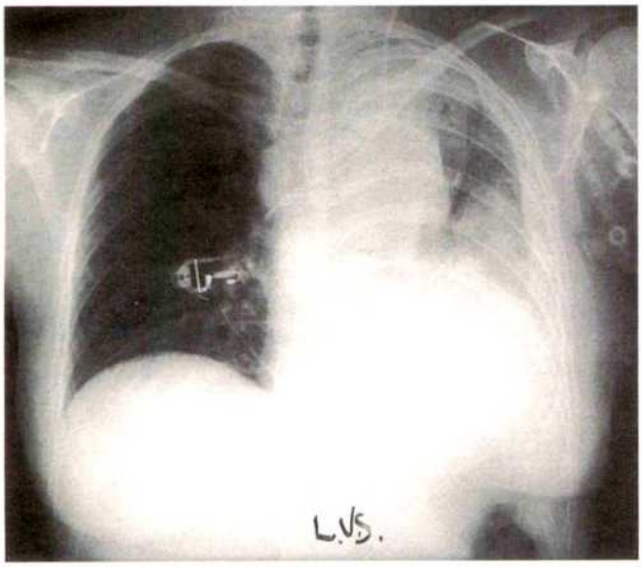

Fig 1 Case 1: the chest radiograph showed alveolar opacities in the left lung, stenosis of the left main bronchus and a suspected aortic aneurysm.

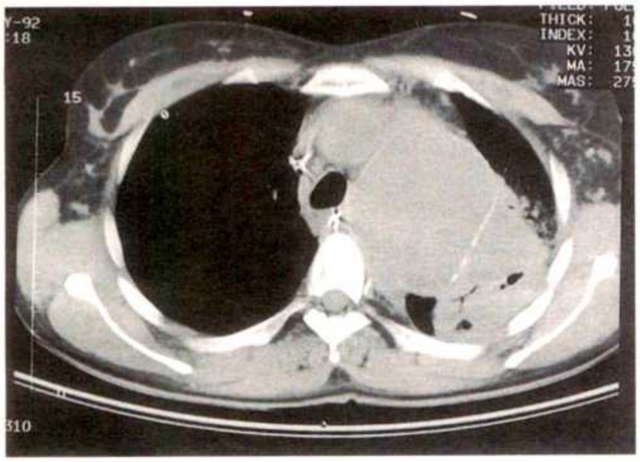

Fig 2 Case 1: the CT scan was diagnostic and showed an aneurysm of the descending aorta, with a calcified aortic wall and suspected rupture into the lung.

Upon admission she was intubated; however, attempts to insert a double-lumen tube failed because of stenosis of the left main bronchus. Chest radiography revealed opacities in the left lung (Fig. 1). Because of recurrent haemoptysis with an estimated blood loss exceeding 1000 ml, the patient required blood transfusion and fluid replacement. Following cardiovascular stabilization, the patient was transferred to the University Hospital. Fibreoptic bronchoscopy revealed an 80% stenosis of the left main bronchus and bleeding from the left lung. Endotracheal intubation with a right-sided double-lumen tube (Broncho-Cath, Mallinckrodt Medical Ltd, Athlone, Ireland) was accomplished. CT scan showed a large aneurysm of the descending aorta (15 cm diameter) that had ruptured into the upper lobe of the left lung (Fig. 2).

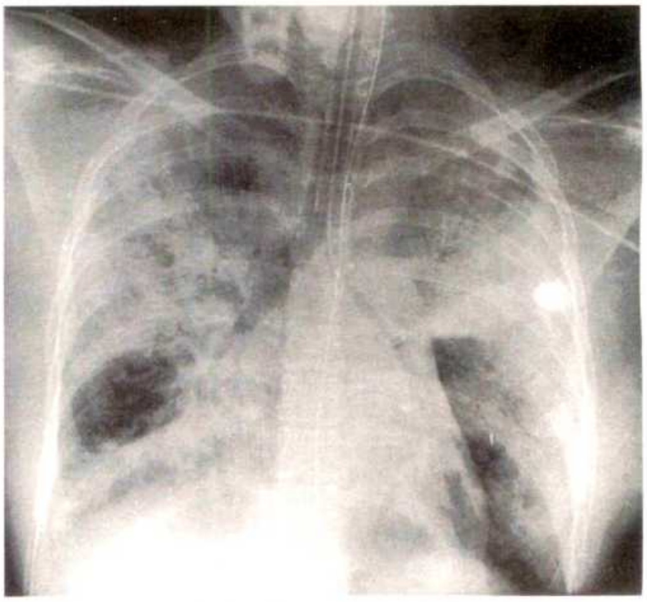

Fig 3 Case 2: chest radiograph showing the double-lumen tube and extensive infiltrates in both lungs resulting from massive bleeding.

Emergency repair of the aneurysm through a left posterolateral thoracotomy was undertaken. The operation was performed on cardiopulmonary bypass and the aorta reconstructed with a Hemashield dacron graft. The rupture in the upper lobe of the left lung was sutured. The patient's trachea was extubated on the day after surgery but shortly afterwards had to be reintubated for a further day. Bronchoscopy and suction were required to clear the airways. The postoperative course was otherwise uneventful, and the patient was discharged on the 18th postoperative day. Two and a half years later the patient underwent uneventful prophylactic surgery with reconstruction of the ascending aorta because of progressive dilatation of the ascending aorta. Histological examination of the resected aneurysm revealed atherosclerosis but no signs of polyarteritis nodosa. On follow-up 5 yr later she remained free from haemoptysis.

Patient 2

A 21-yr-old, previously healthy woman was admitted to her local hospital with massive haemoptysis that started suddenly 2 h prior to admission. On admission she was in haemorrhagic shock and received a 2000 ml blood transfusion. Her trachea was immediately intubated with a single-lumen endotracheal tube. Chest radiography and CT scan showed extensive alveolar infiltrates in both lungs. Emergent fibreoptic bronchoscopy failed to localize the side of bleeding because of flooding of the field with blood.

The patient was transferred to the University Hospital. Upon admission she was haemodynamically stable but presented with an arterial oxygen saturation of 70%. Fibreoptic bronchoscopy was repeated to clear the airways

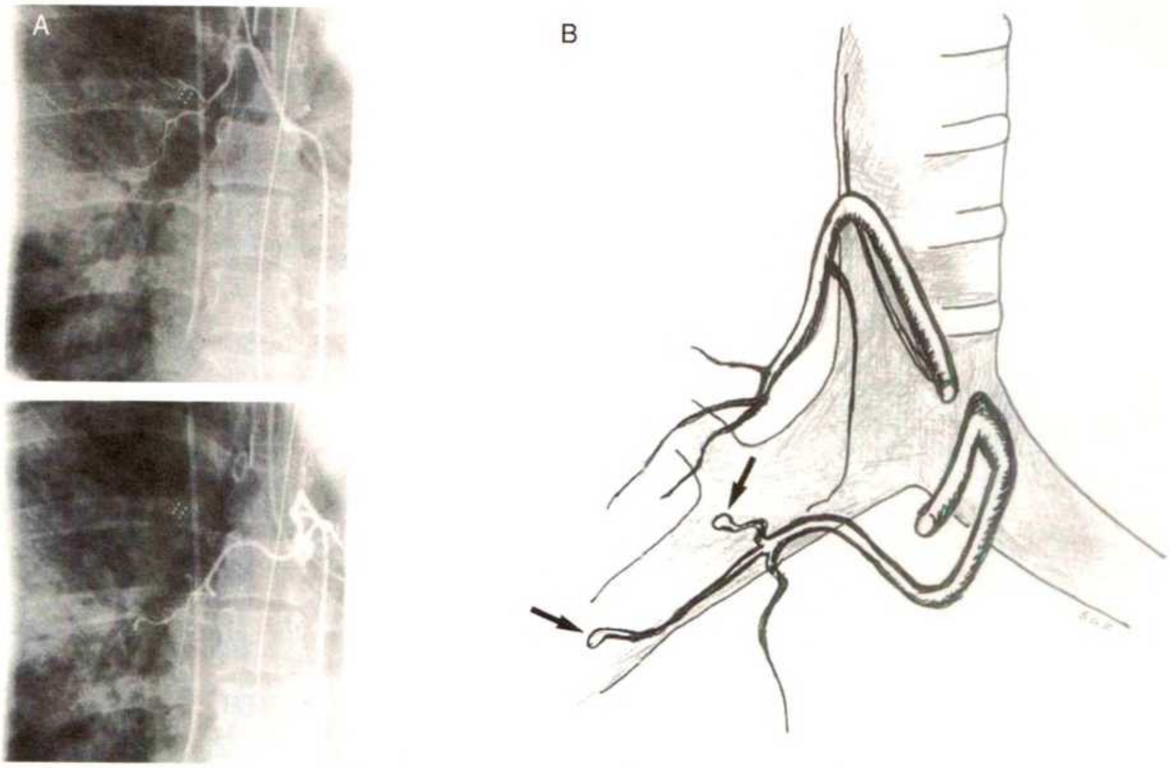

Fig 4 (A) Selective angiography revealed a suspected bleeding from one of the bronchial arteries (bottom), and one normal bronchial artery (top). (B) Schematic drawing; arrows show two aneurysmal dilatations.

of blood and clots, and to localize the source of bleeding. A slightly elevated bluish structure in the right main stem bronchus was found, which was thought to be a vascular malformation. After intrabronchial infusion of epinephrine, tranexamic acid and iced saline lavage, the bleeding diminished. Thereafter a left-sided double-lumen tube (Broncho-Cath, Mallinckrodt Medical Ltd, Athlone, Ireland) was sited (Fig. 3). To reduce the risk of rebleeding, the patient also received desmopressin and tranexamic acid systemically.

Selective bronchial and intercostal artery angiography, aortography and bilateral angiography of the internal thoracic arteries were performed. They revealed two small aneurysmal dilatations and confirmed the suspicion of bleeding from a vascular malformation of the bronchial arteries (Fig. 4). An intimal dissection of the bleeding bronchial artery was caused during attempts to achieve therapeutic embolization. This, however, permanently stopped the bleeding.

The patient required prolonged mechanical ventilation and even ECMO was considered because of hypoxaemia. However, the patient slowly improved and was discharged to the ward after 34 days in the ICU. Later evaluation for a systemic generalized disorder or hereditary trait was negative. It was assumed that the bleeding had resulted from congenital aneurysmal malformations of the bronchial artery. The patient was in good health on 3-yr follow-up.

Discussion

These case reports illustrate the importance of respiratory management and early diagnosis for correct definitive treatment in life-threatening haemoptysis. Death from haemoptysis is rarely caused by exsanguination, but rather by asphyxia resulting from flooding of the airways and alveoli with blood.[6] In our first patient the source of haemoptysis was a ruptured aneurysm of the descending aorta. The second case illustrates a typical cause of massive haemoptysis in young healthy individuals. The clinical course was complicated because of the magnitude of bleeding from the respiratory tract, which initially also threatened the circulatory state of the patient and caused protracted pulmonary dysfunction requiring mechanical ventilation for a month.

The definition of massive haemoptysis varies from 100 to 600 ml of blood loss per 24 h.[1–4 6–8] In our opinion, quantification of haemoptysis may be difficult and, from a clinical point of view, such criteria are not useful. Obviously, haemoptysis that jeopardizes respiratory function should be treated as a medical emergency.

Initial management

The first priorities in treating the patient with life-threatening haemoptysis are to maintain the airway, optimize oxygenation and stabilize the haemodynamic status. Intubation with a single-lumen endotracheal tube is recommended until the bleeding is localized. In patients with lateralized or localized persistent bleeding, immediate control of the airway may be achieved by insertion of a double-lumen endobronchial tube to isolate and ventilate the lungs separately, or by endobronchial tamponade with, for instance, a Fogarty catheter.[7 9–12]

Selective main-stem intubation into the uninvolved bronchus to protect the contralateral side is an alternative to the double-lumen tube if the bleeding side is known. However, with this method there is loss of access to the side of bleeding for suctioning and bronchoscopic examination. The need to clear the airways of blood and clots should influence the decision in the choice of tubes, as clearance of blood is more difficult through the double-lumen tube. Furthermore, a normal fibreoptic bronchoscope cannot be introduced through a double-lumen tube and the risk of occlusion by clots must be considered. Our second patient first received a single-lumen endotracheal tube and later, when the bleeding source had been identified, a double-lumen tube was introduced.

When the side of bleeding is identified it is generally accepted that the patient should be placed with the bleeding side down to prevent aspiration into the uninvolved lung. Systemic therapy directed at improving coagulation deserves consideration. Also, bronchoscopy may be useful for topical haemostatic treatment.[13]

Diagnostic procedures

Occasionally in life-threatening haemoptysis the treatment has to be based on presumptive, rather than conclusive, diagnosis. It is essential to achieve early identification of which lung or lobe/segment is the source of bleeding.

Bronchoscopy, preferably during active bleeding, should be performed to lateralize the bleeding side, to identify the part of the lung that may have to be urgently excised and, if possible, to identify the cause of the bleeding.[7] Rigid bronchoscopy obviously provides better scope for suctioning but does not generally allow visualization of upper lobes and peripheral lesions. The two methods of bronchoscopy can be used in conjunction with one another by passing the fibreoptic bronchoscope through the rigid instrument.[7] In our first patient, the bleeding lung was identified by means of fibreoptic bronchoscopy; in the second, a presumptive diagnosis was made at the second attempt. Major ongoing bleeding in the lungs can render it impossible to identify or even lateralize the bleeding with fibreoptic bronchoscopy. In both patients, however, fibreoptic bronchoscopy contributed to the successful management of the respiratory tract. The choice of bronchoscopy method depends not only on the situation of the patients but is also influenced by availability of special equipment and expertise. Both our patients were intubated. We therefore considered it advisable to use fibreoptic bronchoscopy. Furthermore, fibreoptic bronchoscopy can be performed at the patient's bedside. However, as mentioned earlier, the availability of expertise determines the method in the immediate management of these patients. Use of the rigid bronchoscope is declining and fewer institutions are now providing training in this technique.[7] Repeated fibreoptic bronchoscopy with instillation of cold epinephrine–saline in intubated patients with life-threatening haemoptysis was successful in 6 out of 7 patients.[13]

Chest radiography and CT scan are also useful diagnostic tools. In our first patient a CT scan demonstrated an aneurysm of the descending aorta that had ruptured into the left lung (Fig. 2). However, the site of intra-bronchial haemorrhage is localized with reasonable confidence in only 63% by a combination of these diagnostic techniques.[1]

The lungs have a dual vascular supply, being served by both the pulmonary and bronchial circulations. Selective bronchial arteriography is an important diagnostic technique with therapeutic applications in these cases.[14] In our second patient, bronchial arteriography confirmed the suspicion of a vascular malformation. Occasionally, pulmonary angiography has to be considered, such as in suspected pulmonary embolism or Rasmussen's aneurysm.[15 16]

Echocardiography may reveal rare cardiac causes of massive haemoptysis such as bacterial endocarditis or mitral stenosis.[17 18] Infectious, vasculitic and other systemic diseases should not be overlooked in the search for the cause of bleeding.[1 2 19]

Causes and treatment

Outside the Western world, tuberculosis remains the most common cause of massive haemoptysis.[1] The majority of the patients have bronchiectasias or cavitation. In Western countries, however, neoplastic disease of the lung is the most common cause of massive haemoptysis.[6] Other major causes of massive haemoptysis include aspergilloma and bronchiectasias.[6 20]

A history of haemoptysis in association with menstruation suggests pulmonary endometriosis.[21] Haemoptysis in the early postoperative period should suggest the possibility of injury to the pulmonary vessels by a Swan–Ganz catheter.[11 22] Haemoptysis may occur as a late complication of surgical procedures such as pseudoaneurysms after aortic graft surgery or because of retained foreign bodies after pulmonary procedures.[23 24]

Definitive treatment depends on the cause and anatomical localization of massive haemoptysis. As in our first patient, bleeding from large systemic arteries and aneurysms into the bronchial tree necessitate immediate surgery.[17 25 26] Endovascular stents may provide an alternative to surgery in selected cases.[23] Bleeding from bronchial or other small systemic arteries is treated preferably by selective embolization, as was attempted in our second patient.[14 27] A thorough understanding of bronchial arterial anatomy is required to avoid potential complications, in particular transverse myelitis.[28] [29] Immediate control of haemoptysis by bronchial artery embolization has been reported in between 75% and 90% of patients.[14]

In conclusion, massive haemoptysis should be considered as a life-threatening medical emergency. A well co-ordinated strategy involving different medical and surgical specialists is required for successful management. Control of the respiratory tract is the first priority and should be followed by aggressive measures to identify the source of bleeding, and prompt treatment. Because of the high incidence of recurrent haemoptysis, these patients should not be discharged from hospital before the definitive diagnosis and, if possible, definitive treatment.

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Mechanical closure of the vocal cords with the laryngeal mask airway ProSeal™

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We report a case of mechanical closure of the vocal cords with the laryngeal mask airway ProSeal™ (PLMA) in an anaesthetized, paralysed 59-yr-old, 88 kg female undergoing lower-limb vascular surgery. Near-complete airway obstruction developed after a size-5 PLMA was inserted and the cuff inflated with 20 ml of air. Fibreoptic inspection revealed that the PLMA was correctly positioned, but the vocal cords were closed. Withdrawal of air from the cuff and/or moving the head and neck into the sniffing position resolved this problem.

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The laryngeal mask airway (LMA[†]) ProSeal™ is a new airway device with a large double cuff that forms a better seal than the LMA Classic™, and a drainage tube designed to: (i) protect against regurgitation; (ii) facilitate passage of a gastric tube; (iii) reduce the risk of gastric insufflation; and (iv) facilitate the detection of malposition as air leaking up the drainage tube indicates incorrect tip placement.[1] In a preliminary study of 120 patients, our group reported a first-time successful insertion rate of 90% and an overall successful insertion rate of 100%, all failures being associated with either difficulty manoeuvring the cuff into the pharynx or malposition.[2] We describe a case of mechanical closure of the vocal cords with the PLMA that occurred despite easy placement and correct positioning.

Case report

A 59-yr-old, 88 kg, ASA III female presented for lower-limb vascular surgery expected to take 2 h. Her medical history included non-insulin-dependent diabetes mellitus and peripheral vascular disease. She did not wish to have a regional anaesthetic. Preoperative airway assessment was unremarkable. Anaesthesia was induced with midazolam 1.5 mg, fentanyl 75 µg and propofol 90 mg, and maintained with sevoflurane 1–3% in 33% oxygen and nitrous oxide. Muscle relaxation was with rocuronium 40 mg. Face mask ventilation was easy without the need for a Guedel oropharyngeal airway. A size-5 PLMA was inserted easily without the introducer and the cuff inflated with 20 ml of air. The PLMA was connected to the circle anaesthesia breathing system and manually assisted breathing commenced; however, there was near-complete airway obstruction, with tidal volumes of approximately 100 ml and peak airway pressures of >30 cm H_2O without oropharyngeal air leak. The built-in bite block was between the teeth and there was no air leak from the drainage tube, suggesting correct placement. Fibreoptic inspection down the airway tube further suggested that the cuff was correctly placed because: (i) the epiglottis was within the bowl, but it was not downfolded; (ii) a full view of the vocal cords could be obtained; and (iii) the oesophageal inlet could not be seen. However, the vocal cords were almost completely closed. Before removal of the PLMA, the head and neck were moved from the neutral to the sniffing position by applying chin lift, which resulted in a sudden and complete relief of the obstruction, with tidal volumes of 700 ml and peak airway pressures of <20 cm H_2O. To investigate this phenomenon, we observed the vocal cords and the epiglottis in the sniffing position (no obstruction) and the neutral position (obstruction) on several occasions. In the neutral position, the vocal cords were closed and the anteroposterior diameter of the glottic inlet reduced. In the sniffing position, the vocal cords were open and the anteroposterior diameter of the glottic inlet increased. We also found that adding air

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to the cuff caused the vocal cords to close and the anteroposterior diameter to decrease; removing air from the cuff caused the vocal cords to open and the anteroposterior diameter to increase. Fibreoptic inspection down the drainage tube revealed mucosal tissue in both the neutral and sniffing position (suggestive of correct tip placement); this was subsequently confirmed by easy passage of a gastric tube into the stomach. Surgery was completed using the PLMA with the head and neck in the sniffing position. Oxygen saturation remained >90% during the above sequence of events. There were no other perioperative problems.

Discussion

Three malpositions have been described for the PLMA. The first is when the PLMA is not inserted deeply enough, resulting in the tip sitting mid-pharynx. This results in air leaking up the drainage tube during positive-pressure ventilation and a poor seal. The second is when the PLMA tip impacts against the glottis. This results in airway obstruction and air leaking up the drainage tube.[1] A third malposition is when the tip of the PLMA cuff is folded posteriorly.[3] This results in failure of the drainage tube to perform its intended functions, but it may have no impact on seal or ventilatory function. In our case, the PLMA was correctly positioned and had a good seal, but it failed to function as a ventilatory device because of closure of the vocal cords.

The pathogenesis of vocal-cord closure was probably mechanical rather than physiological as the patient was paralysed and the vocal cords reacted to changes in cuff volume and head and neck position. We found that vocal-cord closure was also associated with a reduction in the anteroposterior diameter of the glottic inlet. We postulate that the mechanism of vocal-cord closure is that the PLMA cuff compresses the glottic inlet along the anteroposterior axis and reduces the tension of the vocal cords. This allows the arytenoid cartilages to rotate inwards and the vocal cords to close. Withdrawing air from the cuff and moving the head and neck into the sniffing position reduces the compressive force against the glottis and allows the arytenoids to rotate outwards and the vocal cords to open. Adopting the sniffing position probably reduces the compressive force by increasing the anteroposterior diameter of the pharynx.[4] Interestingly, mechanical closure of the vocal cords has been reported with the classic LMA in association with cricoid pressure, and a similar mechanism proposed.[5] Moving the head and neck into the sniffing position to correct mechanical vocal-cord closure should not be attempted if the patient has an unstable cervical spine.

One of the authors (JB) has noted mechanical vocal-cord closure occurring in 4 of 915 (0.4%) paralysed patients managed with the PLMA. We speculate that the larger distal cuff of the PLMA may cause more compression of the glottic inlet than the LMA for a given cuff volume. However, the performance of the PLMA as a ventilatory device appears to be similar to the LMA in healthy female patients.[6] A well-known cause of mechanical airway obstruction with the LMA is downfolding of the epiglottis.[7] Although a degree of epiglottic downfolding has been seen in 17% of patients with the PLMA, it rarely causes airway obstruction.[2] This is probably because a downfolded epiglottis rests on the drainage tube and the accessory vent provides a clear passage for gas underneath the drainage tube. However, if the epiglottis is completely folded across the glottic inlet, airway obstruction can occur. Interestingly, epiglottic downfolding will also be improved by moving the head and neck into the sniffing position.[8]

We used the size-5 PLMA in this female patient and inflated the cuff with 20 ml of air. It is possible that selection of a small size and/or use of a smaller cuff volume would have prevented this problem. However, the size-5 PLMA is recommended for adults of 70–100 kg[9] and 20 ml of air is only half the maximum recommended cuff volume. The size-5 LMA has been shown to be suitable for females.[10,11]

In summary, we report a case of mechanical closure of the vocal cords with the PLMA that occurred despite easy placement and correct positioning. We recommend withdrawing air from the cuff or moving the head and neck into the sniffing position to resolve this problem.

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Infected mediastinitis secondary to perforation of superior vena cava by a central venous catheter

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We describe the first case of infected mediastinitis associated with central venous catheter insertion. The rare occurrence of this complication may be explained by the fact that it results from central venous catheter-related bloodstream infection and catheter perforation of superior vena cava. The symptoms of this complication (chest pain, dyspnoea) are not specific. Diagnosis should be confirmed by chest x-ray and computerized tomography which show hydromediastinum and pleural effusion. Removal and subsequent culture of the catheter tip will confirm infection. Appropriate antibiotic therapy, guided by sensitivities of the cultured organisms, should be commenced. Any pleural effusion should be drained by thoracocentesis, and the pleural fluid cultured. In case of fever, bacteraemia or shock, a thoracotomy to drain mediastinal and pleural effusions may be considered.

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Central venous catheters are being used widely and increasingly in modern hospitals. We describe a case of iatrogenic infected mediastinitis after superior vena cava perforation by a central venous catheter in a patient with Crohn's disease.

Case report

A 50-yr-old woman with a previous history of colectomy for Crohn's disease, chronic obstructive pulmonary disease (COPD), obesity and pulmonary embolism (October 1998), presented in December 1998 with a relapse of her Crohn's disease. She had a single lumen catheter inserted into the right subclavian vein in order to start parenteral nutrition. Full aseptic precautions were taken during insertion and blood flowed freely back through the catheter.

Three days later, the patient developed right upper chest pain of sudden onset, dyspnoea and a temperature of 38°C. A chest x-ray showed a right pleural effusion and a widened mediastinum. Pulmonary angiography ruled out a new pulmonary embolism. Computerized tomography (CT) showed a right pleural effusion and a widened mediastinum with enhanced density and 'air pockets' (Fig. 1). Later the same day, she became even more unwell with severe dyspnoea, hypotension and hyperthermia. Her trachea was intubated and mechanical ventilation of the lungs was started. Norepinephine was required to maintain her blood pressure.

She was then referred to the thoracic surgery intensive care unit (ICU) with the diagnosis of mediastinitis and septic shock. A triple lumen catheter was inserted into the left subclavian vein. The catheter in the right subclavian vein was not removed. Chest x-ray showed the catheter in the left subclavian vein but not in the right subclavian vein: there was a right pleural effusion and a widened mediastinum (Fig. 2). Repeated blood cultures were drawn and broad spectrum antibiotics started (piperacillin/tazobactam, isepamicine). Bronchoscopy and oesophagoscopy ruled out the likelihood of oesophageal or tracheal tear. A right thoracotomy was then performed. It showed a dissection of the mediastinum with an effusion of a milky fluid (about 2 litres). This fluid came from the tip of the right central venous catheter which was situated in the mediastinum. Mediastinal and pleural effusion were drained. Blood, mediastinal and pleural effusions cultures grew the same methicillin-resistant *Staphylococcus aureus* (MRSA).

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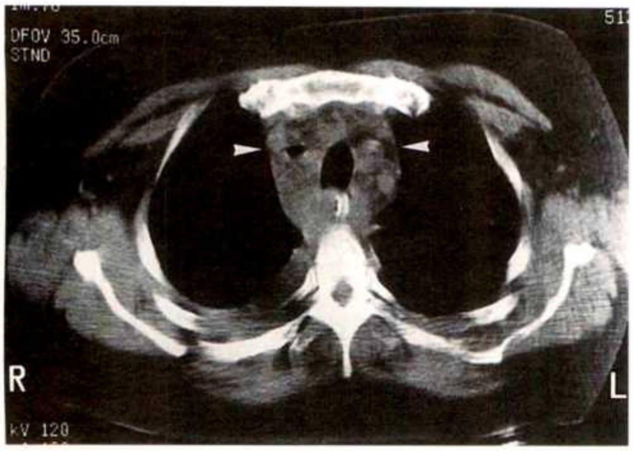

Fig 1 Computerized tomography showing a widened mediastinum with enhanced density and 'air pockets'.

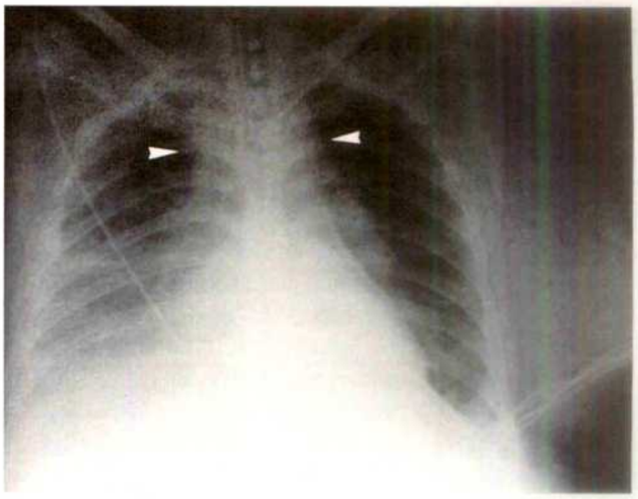

Fig 2 Chest radiograph showing a widened mediastinum, the left catheter (but not the right) and a right pleural effusion.

Unfortunately, there was no catheter tip culture. The presence of triglyceride (128 mmol litre^{-1}) in the mediastinal fluid confirmed hyperalimentation fluid extravasation. We concluded that the patient developed a MRSA mediastinitis and a septic shock secondary to superior vena cava perforation by an infected central venous catheter. Piperacilline/tazobactam and isepamicine were replaced by vancomycin and fosfomycin. At first, the patient's temperature increased intermittently. Bronchoalveolar lavage, urine and faecal cultures were negative for MRSA. CT revealed no deep abscess. Finally, the patient became afebrile, was weaned from the mechanical ventilator and discharged from the ICU on day 14. All antibiotics were discontinued on day 21. She was discharged 15 days later. Altogether, the patient had been in hospital for 6 weeks.

Discussion

This case history is the first that has been reported of infected mediastinitis associated with central venous catheter insertion (according to a Medline search, 1966–2001). Commonly, mediastinitis is secondary to cardiac surgery, oesophageal perforation or cervical infection.[1] In this case, it is believed that the patient developed bacterial mediastinitis complicating perforation of the superior vena cava by a central venous catheter, because:

(i) blood, mediastinal and pleural effusions grew the same MRSA;

(ii) the tip of the central venous catheter was situated in the mediastinum;

(iii) the presence of triglyceride in the pleural fluid confirmed extravazation of the hyperalimentation fluid;[2]

(iv) bronchoscopy and oesophagoscopy discarded the possibility of oesophageal or tracheal fistula.

The rare occurrence of this complication may be explained by the fact that it has to combine two mechanisms. First, there must be central venous catheter-related bloodstream infection, which is not infrequent (2–14 episodes for 1000 catheter days).[3 4] Catheter-related bloodstream infections refer to the isolation of the same organism from a quantitative culture of the distal catheter segment and from the blood of a patient with clinical symptoms of sepsis and no other apparent source of infection.[4] Unfortunately, there was no catheter tip culture and no parenteral nutrition culture. There are, therefore, four possible pathways for this catheter-related infection: external bacterial colonization; internal bacterial colonization; haematogenous seeding of the catheter during bloodstream infection of any origin; or contamination of the fluids or drugs administered intravenously (so-called intrinsic catheter-related bloodstream infection).[4] Involvement of *S. aureus* suggests the likelihood of external or internal bacterial colonization.[4] The attributable mortality of catheter-related bloodstream infection is about 25%.[5 6] Gram-positive cocci are responsible for at least two-thirds of the infections. *Staphylococcus aureus* is responsible for 5–15% of the infections and is associated with a higher rate of complications.[7]

The second mechanism involved is perforation of the superior vena cava by the catheter with extravasation of fluid into the mediastinum. Perforation of the superior vena cava by an i.v. catheter has been widely reported. This may induce haemothorax, hydrothorax, pneumothorax, hydromediastinum and pneumomediastinum.[8–12] The incidence of this complication appears to be about 0.5% of catheter placements, but many catheter tip perforations remain undetected or unreported.[9 10 13] Diagnosis is commonly delayed, which contributes to patient morbidity and mortality.[10]

A few cases of chemically induced mediastinitis from central venous extravasation have been reported. No infectious source has been found in these cases. In one case report, mediastinitis was the result of extravasation of hyperalimentation fluid, after migration of a central venous catheter into the mediastinum.[2] In this case, it was believed that mediastinitis was secondary to chemical irritation by the hyperalimentation fluid, because all cultures (including catheter tip and pleural fluid) were negative. In three cases (one adult and two children), mediastinitis and venous thrombosis were secondary to catheter-related vesicant chemotherapy extravasation.[14 15] In these cases, all the cultures were negative.

Our case emphasizes, once again, that central venous catheterization may induce potentially life-threatening complications. The prevention of catheter-related infected mediastinitis relies on the prevention of catheter-related infection and superior vena cava perforation. Perforation may be the result of mechanical trauma from the catheter tip or chemical damage from infused solutions (hypertonic or vesicant agents).[11] The time from catheter insertion to vascular perforation has a range of 1–60 days.[10] In our case, the delay of three days between the insertion of the catheter and the features of perforation (chest pain, dyspnoea) perhaps favours secondary damage.

There are many factors affecting the risk of perforation by central venous catheters. The more perpendicular the catheter tip to the wall of the vein, the greater the risk of perforation.[9 12 13] Catheters inserted through the left subclavian or internal jugular vein are more at risk of perforation, because the innominate vein forms a right angle to the superior vena cava and the catheter tip may be positioned against the lateral wall of the superior vena cava with a wide angle.[8 10 12 13 16 17] On insertion of a central venous catheter a return of blood through the catheter must be obtained in order to exclude venous perforation by the guidewire, but it does not exclude an extravascular position of the catheter tip, since most catheters have side holes.[8 10] The best test to confirm correct tip placement is a chest x-ray, provided that the catheter is radioopaque (which was not so in our case).

In our case, the patient's symptoms included chest pain and dyspnoea. Chest pain has been reported previously in patients with chemically induced mediastinitis,[2 14] but also in patients with catheter malposition against the sidewall of the superior vena cava.[17] Dyspnoea has been observed only in patients with mediastinitis and central vein perforation.[13 17] The chest x-ray in our case showed a widened mediastinum, as in all but one of the cases of chemical-induced mediastinitis.[2 8 10 13–15] Contrast infusion through the catheter may help the diagnosis (demonstrating extravazation in the mediastinum).[10 13] When mediastinal extravasation occurs, our case emphasizes the need to culture the catheter tip in order to exclude infection. Any pleural effusion should be drained by thoracocentesis, and the pleural fluid cultured. If fever, bacteraemia or shock occurs, a thoracotomy to drain the mediastinal and pleural effusions should be considered.

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Postoperative recovery after inguinal herniotomy in ex-premature infants and the use of caffeine

Editor—Williams and colleagues reported the results of their pilot study comparing sevoflurane to spinal anaesthesia with respect to postoperative recovery after inguinal herniotomy in ex-premature infants.[1] They should be commended on successfully effecting a randomized double-blind study with the minimum of confounding factors. A notable point in this study's validity is the use of the continuous cardiorespiratory monitors in detection of apnoea and bradycardia. In their combined analysis, Coté and co-workers implied that a higher incidence of cardiorespiratory adverse effects will be recorded if continuous and more varied monitoring is instituted.[2]

Methylxanthines, such as caffeine and theophylline, have been used as respiratory stimulants to prevent apnoea in premature infants for over 20 yr, and caffeine is preferred because of its lower toxicity.[3] Caffeine has been advocated as a preventative measure against postoperative apnoea following both general[3] and spinal anaesthesia[4] in the ex-premature infant. Welborn and co-workers describe how a single i.v. dose of caffeine 10 mg given to ex-premature infants during general anaesthesia resulted in a sigificant improvement in rates of apnoea compared to placebo.[5] However, the inhalational anaesthetic drug was not specified in the methodology, but was unlikely to be sevoflurane or desflurane when considering the year of publication. To our knowledge, there have been no studies investigating whether caffeine still confers benefit in at-risk infants when less soluble agents such as sevofluane are used. As such, Williams and colleagues' omission to use caffeine seems reasonable although a large study using modern insoluble agents should include caffeine *vs* placebo as a separate arm.

The Cochrane Review on caffeine advises caution in extrapolating from the small numbers which have actually been studied to routine clinical practice.[6] Possibly because of the small numbers, there were no reports of any baby needing intubation and mechanial ventilation, or any adverse effects from the caffeine. The conclusion is less than definitive. 'caffeine can be used to prevent postoperative apnea/bradycardia and episodes of oxygen desaturation in growing pre-term infants if this is deemed clinically necessary.'

There seems uncertainty as to the clinical significance of episodes of apnoea, hypoxaemia or bradycardia. Indeed, in the study reported by Williams and colleagues all episodes of bradycardia and apnoea were temporally unrelated, all were undetected by real-time apnoea monitoring and nurse observation, and all resolved spontaneously.

As far as pratical advice on the mode of anaesthesia which will reduce the rate of adverse postoperative events, we agree with the authors that the high failure rate (28%) in the spinal anaesthesia group, even in the hands of experienced paediatric anaesthetists, limits the usefulness of this technique.

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Editor—We thank Choi and Davis for their interest in our study.[1]

There is, indeed, some evidence to support the prophylactic use of caffeine in this group of patients. However, in view of the small numbers of infants studied in trials to date and the uncertainty concerning the clinical significance of the cardiorespiratory episodes recorded, we agree with the recent conclusions of the Cochrane Group that there is first a need to determine which infants might benefit most by this treatment before such therapy becomes routine clinical practice.[2] We support the suggestion by Choi and Davis that any future large study using modern potent inhalational agents should include caffeine *vs* placebo as a separate arm. Given the small size of our pilot study and the unpredictable scheduling of surgery, this was not a feasible option for us.

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1 Williams JM, Stoddart PA, Williams SAR, Wolf AR. Postoperative recovery after inguinal herniotomy in ex-premature infants: comparison between sevoflurance and spinal anaesthesia. *Br J Anaesth* 2001, **86**: 366–71
2 Henderson-Smart DJ, Steer P. Caffeine versus theophylline for apnoea in preterm infants. *Cochrane Database of Systematic Reviews* 2001; 3

Do ex-premature infants need mechanical ventilation for inguinal hernia repair?

Editor—We read with interest the paper by Williams and colleagues reporting the postoperative cardiopulmonary complications after sevoflurane or spinal anaesthesia for inguinal herniotomy in ex-premature infants.[1] The authors are to be commended for studying the ideal anaesthetic management of this challenging group of patients. As the study reflects clinical practice, we would be grateful for the authors' comments about our concerns.

First, the authors state that awake regional anaesthesia is potentially stressful for the infant. The stress exists mainly during spinal or caudal puncture. We wonder why sevoflurane was administered for the entire period of surgery instead of for the puncture only? The latter technique would not totally avoid the risk of postoperative apnoea, but does not require tracheal intubation and mechanical ventilation of patients with immature respiratory musculature and underdeveloped central control mechanisms. Mechanical ventilation may be accompanied by a

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high incidence of respiratory complications and might worsen a pre-existing lung pathology[2] By avoiding tracheal intubation, it would probably be possible to decrease the risk of postoperative ventilatory dysfunction.

In our department, we use single dose, caudal epidural anaesthesia in awake infants. Nitrous oxide and Emla cream are used to facilitate caudal puncture. This technique is usually well tolerated by infants[3] Second, a single preoperative dose of paracetamol was used by Williams and colleagues as the only postoperative analgesia. We agree that this combination of caudal anaesthesia and paracetamol often provides analgesia of a sufficient quality and duration, but in some cases more analgesia is required in the first 12 postoperative hours. Third, the cardiopulmonary complications observed in their study may be related to the residual effect of the inhalational agent or to the pain. Neonates often react with bradycardia and/or apnoea in response to a painful stimulus.

Finally, we completely agree with the authors' conclusion. Awake regional anaesthesia in ex-premature infants undergoing inguinal herniotomies may be preferable to general anaesthesia. However, large prospective controlled studies are required for providing safe and adequate anaesthesia to smaller and sicker infants.

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1 Williams JM, Stoddart PA, Williams SAR, Wolf AR. Postoperative recovery after inguinal herniotomy in ex-premature infants: between sevoflurance and spinal anaesthesial *Br J Anaesth* 2001; **86**: 366–71
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Editor—The anaesthetic management of this potentially challengging group of patients varies widely both within and between institutions.[1] The aim of this pilot study was, therefore, to reflect as closely as possible clinical practice at our hospital and explore the hypothesis that the recovery after sevoflurane anaesthesia is comparable with that after spinal anaesthesia, with neither group experiencing an increase in the number of episodes of apnoea, hypoxaemia or bradycardia relative to preoperative levels.[2] By attempting to ensure that both groups were comparable in terms of the duration and intensity of analgesia provided, we hoped to be able to detect in the initial postoperative period any excess cardiorespiratory complications attributable to residual sevoflurane anaesthesia alone. This would not have been possible had we, as proposed by Bouchut and Claris, exposed patients in the spinal anaesthesia group to sevoflurane and/or nitrous oxide at the time of dural puncture only

J.M. Williams
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Downward movement of syringe pumps reduces syringe output

Editor—I read with interest the article by Kern and colleagues entitled 'Downward movement of syringe pumps reduces syringe output'.[1] It illustrated the effects of hydrostatic pressure changes on drug delivery due to changes in the elastic and non-elastic components of syringe pump infusion systems, that is compliance and mechnanical displacement. The article recommends giving drugs at higher flow rates using appropriate dilutions, less concentrated than on the ICU, in any environment where the equipment is moved frequently. It appears that the authors were able to determine their defined target variables correctly. Nevertheless, there seem to be some inconsistencies in the paper.

As the compliance of the system is the key to most of the effects demonstrated, I wonder why the results were not discussed in relationship to it; it is merely stated that 'there is a statistically significant positive correlation between time without infusion and the compliance of the system'. However, the volume shift calculated from the compliance measurements (81–103 µl mm Hg^{-1}) caused by a change in height of 130 cm ($\Delta p \approx 95.4$ mm Hg) is 7.7–9.8 ml (conversion factor: 1 cm H_2O=0.734 mm Hg). This would cause a backflow of blood into the syringe, which is not found clinically, indicating that these values are not correct Furthermore, for these experiments glass capillaries were used, which have a calculated volume of approximately 196 µl, and it could be predicted that only small volume shifts were observed.

Calculating the change in volume caused by lowering the syringe pump (Injectomat-C) in the 'paediatric setting' using the data for 'time with no flow' from Table 1 (hopefully the same as 6=time without efficient infusion for the patient in Figure 3), and the respective flow rate, resulted in volumes in the range of 116 µl to 144 µl, causing a compliance in the range of 1.2 to 1.5 µl mm Hg^{-1}. It is probably not appropriate to calculate system compliance from the change in volume after lowering the syringe, as this results in a pressure increase in the syringe. Some non-reversible mechanical displacement in the pump mechanics may also contribute to the volume loss (non-elastic components). The bolus volume after resetting the syringe to its original high level seems to be a better measure of the elastic components of the system. The remaining missing volume as illustrated in Figure 3 point 8 may account for the non-elastic components i e. non-reversible mechnical displacement of syringe pump mechanics.

I tried to replicate the experiment illustrated by Figure 3 according to the values given for point 6 in this figure, and the slope of the continuous infusion It seems to be the IVAC 770 2 ml h^{-1}adult setting ($\Delta p \approx 58.9$ mm Hg) which is used. Taken from the graph, the bolus volume seems to be 117 µl resulting in a compliance of 1.98 µl mm Hg^{-1}, whereas the compliance given for this system is 103 µl mm Hg^{-1}.

In an *ad hoc* setting, I repeated the experiment with our clinical equipment. I estimated pressure dependent compliances in the range of 1.17 to 2.38 µl mm Hg^{-1} at infusion rates of 2 ml h^{-1} and 5 ml h^{-1} for a system with the capillary shunt of the transducer closed These estimations confirmed the above calculations. This suggests, that, in the paper, a conversion error may have occurred by transforming the infusion rate from ml h^{-1} into µl s^{-1}. Dividing the reported data by 60, equates it with the calculated and estimated compliances.

The strengths of the paper are the clinically relevant target variables which produce guidelines for clinical work. I expect—as no information is given—that the work was done with syringes carefully filled with water or saline, with no air bubbles, as are frequently seen in clinical practice. It is of note that, according to Gas Laws (Boyle-Mariotte Law: $P_1 \times V_1 = P_2 \times V_2$) an air bubble of merely 1 ml may cause an additional volume shift (approximately 115 µl 95 mm Hg^{-1}) in the same range as those described in the paper. This will lead to a marked increase in the target variables of the paper (i.e. the time without accurate infusion to the patient), and will considerably affect its clinical recommendations. However, especially in infants, when several drugs are needed, any increase of the infusion rate is limited. Therefore, if one is concerned about this problem, the clinical practice should be changed to using low compliant syringes, that is small volume syringes, and using low compliant–low volume infusion lines as are common in neonatal practices. Special care must be taken that the syringes are filled carefully without air bubbles.

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[1] Kern H, Kuring A, Redlich U, et al. Downward movement of syringe pumps reduces syringe output. *Br J Anaesth* 2001; **86**: 828–31

Editor—We read with interest Wissing's letter commenting on our article.

Indeed, Wissing correctly identified a conversion error. This occurred while transforming the infusion rate of the syringe pumps for the compliance measurements from ml h^{-1} into μl s^{-1}. The reported compliances therefore have been divided by 60. The corrected results for the compliance of the different systems resulted in identical values for the Injectomat-C and the Perfusor fm of 1.4 μl mmHg^{-1}. The compliance of the IVAC 770 system was greater, at 1.7 μl mmHg^{-1}. There was a statistically significant positive correlation (r^2=0.863, P<0.05) between time without infusion and the compliance of the system. This correlation has been tested again and remained unchanged. We apologize for this error and thank Wissing for pointing it out.

However, the main results of our work are not affected by this mistake. We measured the volume shift ($\Delta v/\Delta p$) correctly in our experiments. Compliance is a calculated value as indicated in the Methods section. However, we would like to emphasize that our model used a fixed pressure of 8 mmHg working against the infusion, which is comparable to central venous pressures encountered in daily clinical practice. This is in contrast to previous investigations which used syringes working against ambient air pressure. We took great care to avoid the occurence of any air bubbles while filling the syringes and lines in our experimental setting. Before starting to take measurements, the eqiupment was visually checked for gas bubbles.

The main goal was to investigate systematically the daily clinical observation of haemodynamic instability and sometimes even backward flow in the infusion lines while lowering the height of the syringe pumps towards the end of paediatric cardiac surgery. This question was investigated with the equipment used in daily clinical practice. Obviously, there is equipment available with better elastic properties (compliance). However, we consider the other tubing, which is made for neonatal intensive care purposes, to be too short for daily use in the operating room. We do not think that a broad discussion of all possible elastic and non-elastic components of the infusion systems would increase the clinically relevant information. As we stated, we did not endorse any particular manufacturer or model of infusion device.

Our main conclusion was that, whenever possible, the height of the syringe pumps should not be changed during transport. If changes in the position of the syringe pumps are inevitable, we proposed a drug dilution achieving a flow rate of at least 5 ml h^{-1}. Obviously, this recommendation has to be balanced against possible deleterious effects caused by fluid overload, particularly in paediatric patients.

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Blood pressure manipulation during loco-regional anaesthetic carotid surgery

Editor—We read with interest the three case reports regarding blood pressure manipulation during local anaesthetic carotid surgery.[1] Our experience with over 200 local anaesthetic carotid endarterectomy (CEA) patients, approximately 35% of whom subsequently underwent urgent coronary artery bypass graft (CABG) surgery, is very similar. However, we feel that there are a number of additional points that should be considered.

In patients requiring CABG and CEA, it is our strategy to perform local anaesthetic CEA(s) followed at a later date by the cardiac surgery. In a few high risk patients we found coronary angioplasty and/or stenting of target lesions to be beneficial prior to the staged CEA/CABG.

Cross-clamping usually results in a moderate rise in arterial blood pressure. Whilst the carotid artery is clamped, a subsequent fall in arterial pressure can result in the development of a neurological deficit. Like the authors, we feel pharmacological augmentation of the blood pressure is useful and sometimes reverses the deficit. However, this augmentation clearly increases cardiac work and oxygen consumption, and we have seen angina, and occasionally myocardial infarction and pulmonary oedema, as a direct result of this manipulation.

Angina occurring during the cross-clamp phase will often respond to coronary artery vasodilators. However, an exaggerated fall in blood pressure can then occur and this can be associated with neurological deterioration. We have encountered two patients who were already on high doses of i.v. glyceryl trinitrate who developed angina when cross-clamped. In these two patients, we found insertion of a carotid artery shunt led to immediate relief of their angina, as the arterial pressure returned to pre-clamp levels

Our practice is to use near infrared spectroscopy to measure cerebral oxygenation during awake carotid surgery Cross-clamping usually results in a fall in cerebral oxygenation, and this fall is partially reversed by raising the blood pressure, which adds further support to blood pressure augmentation during the cross-clamp phase.

We believe that local anaesthetic carotid surgery allows optimal and integrated treatment of both the neurological and cardiac aspects of these patients. Close cooperation between the vascular anaesthetist, the vascular surgeon, the cardiologist, the cardiac-surgeon and the patient is clearly vital in this challenging group

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[1] Stoneham MD, Warner O. Blood pressure manipulation during awake carotid surgery to reverse neurological deficit after carotid cross-clamping. *Br J Anaesth* 2001, **87**: 641–4

Editor—Thank you for the opportunity to reply to the letter from Imray and colleagues, which appears to be generally supportive of regional carotid surgery. I agree with them and, indeed, discussed in the case report the fact that angina may be precipitated perioperatively in this high-risk group of patients However, I am curious as to whether the two patients they described, who developed angina following carotid cross-clamping, also developed neurological dysfunction, as shunting is not a conventional therapy for angina and is certainly not without risk itself.[1]

Imray and his anaesthetic colleagues have also rasied a different issue—namely the treatment of patients with combined carotid and coronary arterial disease. In Oxford, our cardiac surgeons also request that patients with symptomatic carotids and coronaries have endarterectomy performed under regional anaesthesia before they have their coronary artery surgery. This has proved very successful in 20 or so patients, thus far. However, this is not the only solution and there are certainly centres in which patients with those two conditions are operated on synchronously under general anaesthesia.[2]

Finally, the authors do not say what information they gain from using near infrared spectroscopy in addition to that which the conscious patient provides.

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1 Jacobowitz GR, Rockman CB, Lamparello PJ, *et al* Causes of perioperative stroke after carotid endarterectomy· special considerations in symptomatic patients. *Ann Vasc Surg* 2001; **15**: 19–24
2 Farooq MM, Reil TD, Gelabert HA, et *al* Combined carotid endarterectomy and coronary bypass. a decade of experience at UCLA. *Cardiovasc Surg* 2001, **9**. 339–44

Sedative and analgesic practice in the intensive care unit

Editor—I read with interest Soliman, Melot and Vincent's European survey of sedative and analgesic practice in the intensive care unit.[1] This article demonstrated considerable international differences in the use of drugs for this purpose.

However, one factor that was not investigated in the survey or discussed in the accompanying editorial was the use of physical restraints. Whilst restraints are very rarely used in the UK, they are more common in the USA,[2] Canada,[3] Australasia and continental Europe.

Because of the recognized dangers of chemical oversedation, it is tempting to realize the use of physical restraints in UK units However, this may not be straightforward. Notwithstanding the moral and ethical complexities, physical restraints are associated with a number of disadvantages. They have not been shown to decrease the incidence of self-extubation,[4] and they are associated with certain types of physical injuries.[5] More worryingly, physical restraints have also been associated with sudden death.[6]

In all probability, there are many other reasons why sedation practice varies in Europe and the rest of the world, but the use of physical restraints should be considered with investigating these differences.

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5 Neufield RR, Libow LS, Foley WJ, *et al.* Restraint reduction reduces serious injuries among nursing home residents. *J Am Geriatr Soc* 1999; **47** 1202–7
6 Miles S. A case of death by physical restraint. *J Am Geriatr Soc* 1996; **44**: 291–2

Editor—Dr MacKillop raises an interesting subject when referring to the use of physical restraints. This issue was not addressed in our study, largely because the survey focused on differences in drug selection, rather than the use of sedation *per se*.

In addition, the definition of 'physical restraint' is broad and subjective, and it would have been difficult in a short questionnaire of this type to retrieve valuable information from a simple yes/no question. If asked whether physical restraints were used in their ICU, the vast majority of, if not all, physicians would have to reply 'sometimes'. Further questions would then be needed to define how often and in which patients. Moreover, individual physicians will have different theories as to what constitutes physical restraint, founded on previous experience and background, local practice, and cultural, religious and moral beliefs.

Furthermore, while Dr MacKillop suggests that the use of physical restraints may be used in place of, or to limit, sedation, it is equally possible that some restrained patients may need more sedation due to their agitation at being restrained. There is, in fact, very little published data regarding the use of physical restraints in adult intensive care unit patients—a quick Medline search drew only 10 related publications in the last decade[1–10]—and this interesting topic certainly warrants further study.

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1 Happ MB, Kagan SH, Strumpf NE, Evans LK, Sullivan-Marx E. Elderly patient reports of physical restraint experiences in intensive care units. *Am J Crit Care* 2001; **10**.168–71
2 Frezza EE, Carleton GL, Valenziano CP. A quality improvement and risk management initiative for surgical ICU patients· a study of the effects of physical restraints and sedation on the incidence of self-extubation. *Am J Med Qual* 2000; **15**: 221–5
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4 Bower F, McCullough C. Restraint use in acute care settings: Can it be reduced? *J Nurs Adm* 2000; **30** 592–8
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Allergy to chlorhexidine-coated central venous catheters revisited

Editor—We read the case report by Stephens and colleagues[1] with interest as the scenario they describe parellels our own recent experiences of the same phenomenon.

A 51-year-old male presented for corpectomy of the 4th cervical vertebra, for relief of severe intractable cervical spondylosis Also of note in his medical history was peripheral neuropathy secondary to alcohol abuse, and a chronically infected knee replacement. His anaesthetic history was unremarkable: he had had several general anaesthetics for orthopaedic procedures over the preceding 5 yr. He was receiving gabapentin and regular oral morphine for analgesia. The patient described developing a rash subsequent to receiving penicillin many years previously but otherwise had no known allergies or history of atopy. All routine preoperative investigations were normal.

He was unpremedicated. After preoxygenation, anaesthesia was induced uneventfully with infusions of propofol and remifentanil. His haemodynamic variables were stable; arterial pressure was 105/65 mm Hg and pulse rate 65 beats min^{-1}. Tracheal intubation was effected after a bolus of atracurium 40 mg followed by an infusion. A left radial arterial line was sited, followed by a central venous catheter (Arrow-Howes$^{\text{TM}}$ multi-lumen central venous catheterization set with ARROWg^{+} and Blue® Catheter, Arrow, Reading, USA) into the left internal jugular vein. The skin was prepared in both cases using a solution of chlorhexidine 0.5% in spirit (Hydrex®, Adams, Leeds, UK). As the central line was being inserted, the patient's systolic arterial pressure suddenly dropped from 105 mm Hg to 30 mm Hg with a tachycardia of 120 beats min^{-1}. Simultaneoulsy, the patient developed a widespread erthematous rash. All anaesthetic agents were stopped and a midazolam infusion commenced at 10 mg h^{-1}. Blood pressure responded poorly to boluses of vasopressors (metaraminol 3 mg, epinephrine and norepinephrine 100 μg each) followed by infusions of epinephrine and norepinephrine (at rates of 500 $\mu\text{g h}^{-1}$ and 1200 $\mu\text{g h}^{-1}$ respectively) and a crystalloid infusion. Bronchospasm was not apparent. The patient was given hydrocortisone 200 mg and chlorphenıramine 10 mg intravenously. A provisional diagnosis of anaphylaxis to either latex or one of the drug infusions was postulated, and all monitoring equipment plus the tracheal tube were replaced with the latex-free variety. Over the ensuing 2 h the rash and requirement for inotropes disappeared. The patient was transferred to the high-dependency unit and extubated uneventfully. Blood was taken 1 h after the onset of symptoms for estimation of tryptase and immunoglobulin specific for mast cell or latex. Surgery was postponed pending these results and skin prick tests.

Mast cell tryptase was elevated at 16.8 $\mu\text{g litre}^{-1}$ (normal range 0–12 $\mu\text{g litre}^{-1}$), more suggestive of an anaphylact*oid*, rather than anaphylactic reaction. This result corroborated the negative results of skin prick tests for all the agents administered. A RAST test to latex was also negative. A speculative diagnosis of a non-IgE mediated (anaphylactoid) reaction to atracurium was postulated.

The patient presented for surgery 4 weeks later and on this occasion was premedicated with dexamethasone 4 mg four times daily for 24 h preoperatively. Anaesthesia was again induced with propofol/remifentanil infusions, but tracheal intubation was facilitated with vecuronium instead of atracurium. After 25 min of anaesthesia and during insertion of a left internal jugular central venous catheter (of the same type as used previously), there was a marked drop in the patient's systolic arterial pressure from 150 to 30 mm Hg. Anaesthesia was promptly discontinued. Again, hypotension responded slowly to vasopressors and fluid administration (metaraminol 5 mg incrementally plus epinephrine 100 μg bolus followed by 200 $\mu\text{g h}^{-1}$ infusion). The accompanying rash was less pronounced, and bronchospasm did not occur. Surgery was again postponed and the patient was extubated uneventfully approximately 1 h later.

As well as repeat blood tests, subsequent investigations included echocardiography, CT scan of the left carotid bifurcation, and urinary catecholamines. Mast cell tryptase was normal on this occasion (9.7 $\mu\text{g litre}^{-1}$) as were all of these tests. A raised serum total IgE of 1178 kU litre^{-1} was the only abnormality detected, suggesting an atopic tendency.

The temporal relationship on both occasions between central venous catheter insertion and cardiovascular collapse led to suspicion that some component of the catheter was responsible for the reactions. The same catheter kit was used on each occasion and is coated with chlorhexidine. Five months later, skin prick testing with chlorhexidine 1% resulted in a characteristic sustained wheal and flare response, strongly suggesting an IgE-mediated sensitivity. The patient subsequently underwent uneventful surgery following premedication with hydrocortisone 100 mg qds, chlorpheniramine 10 mg tds and ranitidine 150 mg bd for 24 h preoperatively, and strict avoidance of chlorhexidine exposure.

Our case parallels that of Stephens and colleagues in that two episodes of pronounced refractory cardiovascular collapse accompanied the insertion of a chlorhexidine-coated central venous catheter. Bronchospasm was not a feature in either case, nor of the two reported Japanese cases.[2 3] Whereas the other cases described were skin prick tested for chlorhexidine following their first reaction, there was no precedent in our patient's history to lead us to suspect chlorhexidine as a possible causative agent.

The mast cell tryptase level within the normal range following the second reaction may be explained by the 24 h of preceding steroid therapy on that occasion. The positive skin prick test for chlorhexidine suggests an anaphylactic, rather than anaphylactoid reaction. Clinically, the precise immunological basis of the observed reactions is less important than the absolute avoidance of the precipitating agent. We advocate others to exercise a high degree of suspicion for chlorhexidine allergy if faced, in future, with similarly unusual circumstances.

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1 Stephens R, Mythen M, Kallis P, Davies DWL, Egner W, Rickards A. Two episodes of life-threatening anaphylaxis in the same patient to a chlorhexidine-sulphadiazine-coated central venous catheter *Br J Anaesth* 2001; **87**: 306–8

2 Terazawa E, Nagase K, Masue T, *et al.* Severe anaphylactic reaction due to a chlorhexidine-impregnated central venous catheter. *Masui* 1998, **47**: 556–61

3 Oda T, Hamasaki J, Kanda N, Mikami K Anaphylactic shock induced by an antiseptic-coated venous catheter. *Anesthesiology* 1997, **87**· 1242–4

Editor—We thank Drs Pittaway and Ford for reporting their similar experience in another case of suspected chlorhexidine allergy and we are grateful for the opportunity to add some further comments.

This case adds further weight to the source of the problem being with the central venous catheter, or its coating. We would again urge great caution when using 'coated catheters', which have an identified package insert warning that these catheters are not to be used in individuals who are thought to be sensitive to chlorhexdine. It would appear that had it not been for the presence of intra-arterial monitoring and aggressive resuscitation, the outcome in all of these cases may not have been so favourable In trying to reduce the incidence of central venous line sepsis, we have introduced a greater risk of sudden and profound anaphylaxis with these particular central venous catheters.

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Outcome measures

Editor—I read with interest both editorials[1 2] and the article by Hall and colleages[3] that appeared in the journal. Both editorials identify the need for continued efforts to define the issues (both clinical and service) that contribute to perioperative management, and impact ultimately on patient outcome. Carli and Mayo argue that, without effective ways to define, measure, and analyse outcome, we are limited in our attempts to identify the factors that significantly contribute to patient recovery. Outcome is heavily influenced by the constraints placed upon it by the prevailing healthcare system and administrative culture. Studies that look to relate purely biological variables without consideration of these issues are likely to be limited in their conclusions and practical impact. Severn, in his article on anaesthesia for the elderly, emphasized the importance of coordinated intervention, citing two case reports to support the deficiency in our current service.[4 5] Both editorials comment on the important contribution of social factors to the quality of outcome, and the need for coordinated care to achieve effective management. In this regard, I was disappointed that more was not made of the importance and need for service development. Neither article speculated on how coordinated management should be achieved, missing the opportunity to highlight the potential of an integrated preassessment service in achieving directed management of both the patient and the clinical resource, and hence influencing outcome. Specialty perspective has for too long limited the potential of surgical preassessment; this has created a poorly integrated hospital-based service focused on the surgical specialty instead of the patient. In this format coordinated intervention is difficult to achieve, and the system is subject to the negative effects of parallel working practices. The provision of a standardized, integrated preassessment service designed to coordinate both clinical and social aspects of care, is far more likely to be capable of creating the necessary conditions to allow the real impact of biological factors on surgical outcome to be assessed.

One way to achieve this for elective surgical patients, would be to adopt a two stage preassessment process developed from a case management model (the emphasis is on the integration of services, both within the hospital and community):

Stage I Medical optimization (coordinated by anaesthetists).
Stage II Surgical preparation (coordinated by surgeons).

Stage I begins with assessment immediately after the patient is seen in the surgical clinic and added to the operative waiting list. This provides the maximum available time to plan and coordinate care by collaborative working with all of those (within hospital and the community) involved in patient management. Coordinated by a centralized preassessment unit and using an IT based proforma, this format provides the necessary platform for the collection and distribution of relevant information, directing the involvement of other specialities according to patient need. Stage II begins closer to the admission date, and is largely responsible for patient education. A sustainable community element ensures joint follow-up between hospital and community, providing the necessary exchange of information and opportunity for a proactive attempt to achieve coordinated intervention. This is the preassessment model currently being developed in Carlisle, and is the Community Pilot for the National Preassessment Project.

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1 Carli F, Mayo N. Measuring outcome of sugical procedures: what are the challenges? *Br J Anaesth* 2001; **87**: 531–3

2 Severn AM. Time to light the grey touch paper! The challenge of anaesthesia in the elderly. *Br J Anaesth* 2001; **87**· 533–6

3 Hall GM, Peerbhoy D, Shenkin A, Parker CJR, Salmon P. The relationship of the functional recovery after hip arthroplasty to the neuroendocrine and inflammatory responses. *Br J Anaesth* 2001; **87**: 537–42

4 Oliver CD, White SA, Platt MW. Surgery for fractured femur and elective ICU admission at 113 years of age. *Br J Anaesth* 2000; **84**: 260–2

5 Sharrock NE Fractured femur in the elderly: intensive perioperative care is needed. *Br J Anaesth* 2000; **84**: 139–40

Editor—Thank you for the opportunity to reply to Tidmarsh's letter. The editor's brief was to provide a commentary on the state of knowledge of anaesthesia as it pertained to the elderly, using the review by Jin and Chung[1] as a starting point. The editorial mentioned published examples where the perioperative care of the elderly could have been managed better and in a more coordinated fashion, since these examples showed, amongst other things, a lack of knowledge of basic perioperative principles. Tidmarsh is to be commended in his attempts to provide a seamless service and to involve physicians and anaesthetists from the beginning; it is the model to which we all would aspire. However, the reality is that badly coordinated care may only be made worse by increasing specialization, the introduction of shift working, and the implementation of care pathways that dictate that a patient be managed (and discharged) according to fixed protocols. A goal of preassessment is prediction of complication; however, the apparently healthy elderly patient may surprise us with a degree of perioperative cognitive dysfunction, or frank cerebral or cardiovascular morbidity.

I fear that preassessment may not deliver unless the real issues of coordinated perioperative care are simultaneously tackled.

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1 Jin F, Chung F. Minimizing perioperative adverse events in the elderly. *Br J Anaesth* 2001; **87**. 608

The alveolar surface and the geodesic planes hypothesis

Editor—Bangham's commentary[1] on the article by Dorrington and Young[2] is rather unabashedly ill-informed with regard to alveolar surface structure as it is *in vivo*. The issue addressed is alveolar structural stability in the face of surface forces operating at the air-interface according to the law of Laplace, where collapse pressure (P, cm H_2O) is related directly to surface tension (γ, mN m^{-1}) and inversely to radius of curvature (r, μm). In order to eliminate the effect of high surface tension of 23+ mN m^{-1} (Banghan's assumption), Bangham offers his new model of alveolar surface configuration, namely, 'plaques of solid phospholipid separating and initiating a geodesic plane of water, where γ may be as high as 72 mN m^{-1}'. As both the solid and the water sufaces are flat (i.e. r is infinite) P (in Laplace) is virtually zero. Bangham insists further that γ cannot be less than –23 mN m^{-1}, the 'equilibrium γ'.

Bangham's concept fails for many reasons, the essence of which is tied to his declaration that 'unlike bubbles, the alveoli are open to the atmosphere'.[1] To the contrary and as a matter of fact, the alveoli are aerated and structually stabilized by unit ***bubbles***, the ultrathin foam films of which are formed by phospholipid

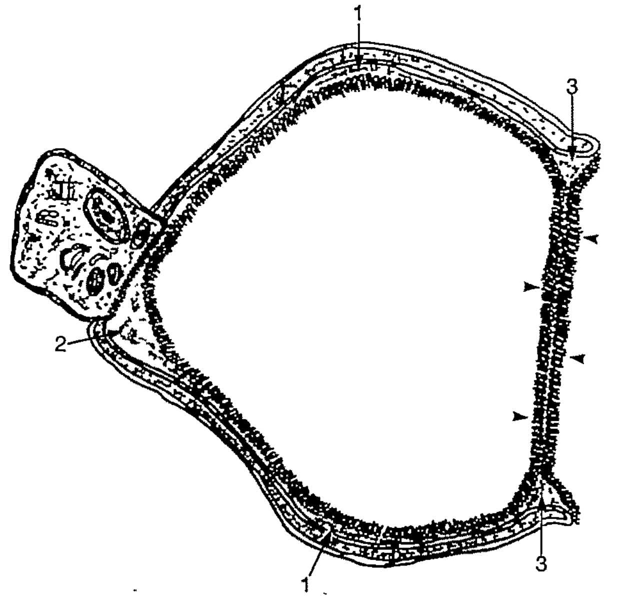

Fig. 1 Drawing of a unit alveolus, aerated and structurally stabilized by its constituent unit bubble, the film of which is a compressed ('solid' phase) monolayer of surfactant molecules (symbols) at the air-interface Underlying liquid is thinnest where the surface is planar, (e.g. to the right and left of 1). It expands as curvature increases (e g at 2). The bubble film apposes a second unit alveolar or ductal film near the alveolar mouth to form a 'classical foam film' to <7 nm thickness (arrowheads) and borders ('Plateau borders') of increased liquid thickness where the two layers bend in opposite directions (3)

surfactants secreted by Type 2 pneumocytes.[3] Curiously, Bangham makes no reference to the many research reports, beginning in 1978,[4] which show by direct inspection of fresh lungs as they exist *in vivo*, that intra-alveolar bubbles and bubble films are the stable infrastructure upon which alveolar function is based (e.g. references 5–7) (Fig. 1). The juxtaposition of bubbles in the acinus (there are no bubbles in conducting airways) establishes the 'alveolar surface network'[3] of ultrathin foam films (to <7 nm thinness) freely permeable to respiratory gases. The network (like foam) is a continuous liquid channel circulating among alveoli; the channel is formed by the discontinuous foam films of the alveolar gas-containing unit bubbles through which gas transfer is effected and structural integrity is established. The bubble film configuration with surfactants in the 'solid' phase eliminates the 'water'–'water vapour' interface that so troubles Bangham.[1] At the same time, it confirms Pattle's *in vitro* observations (namely, bubbles expressed from the lung have near-zero γ), which marked his discovery of lung surfactant.[8] [9]

The bubbles of the alveolar surface network are clearly visible *in situ* at all stages of life (birth through adulthood), at all lung volumes (residual volume through functional residual capacity to total lung capacity), and during all breathing manoeuvres (eupnoea to vital capacity). Bubble renewal *in situ* has been described. bubble film rupture→'collapse' of unit alveolus→ bubble reformation. In the laboratory, bubbles *in situ* are destroyed by virtually all 'routine' processing methods. Hence, they have eluded discovery until recently.[4] However, the alveolar surface network is easily identified both in the fresh, unperturbed lung and following careful preservation techniques in the laboratory.[4–7]

Whereas Dorrington's negative response to Bangham's model[10] is appropriate, both his and Bangham's espousal of an 'open' alveolar surface, planar or otherwise, is without merit, given the normal configuration of the alveolar surface *in vivo*, that is the alveolar surface network.

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Informed consent for regional anaesthesia

Editor—Absalom and colleagues raise the thorny issue of informed consent and regional anaesthesia in their description of nerve injury following local anaesthetic infiltration [1] Although implied consent was given *via* the patient's husband and an interpreter, it is difficult to extend that to cover the full explanation of material risk to the patient, or to knowing that that risk has been understood. The Association of Anaesthetists' guidelines clearly state that no other person can consent to treatment on behalf of this patient.[2]

Patients may well opt for a regional technique, 'when informed of the benefits'. However, as with all invasive procedures, regional anaesthetic techniques require that the patient is fully cognisant of the risk of nerve injury before starting the procedure. The demand for a pain-free recovery is not a reason to compromise on these standards.

In the context of an anxious, partially sedated patient, communicating through her husband, it would seem that the benefit of clear verbal contact was already lost. A situation then arises whereby the patient is neither awake and able to communicate, nor asleep and immobile.

If what is important is the standard of practice and not the practice itself,[3] an inability to secure informed consent coupled with an inability to carry out the epidural insertion awake should lead to careful consideration of the risk/benefit ratio. In this difficult scenario, a balanced general anaesthetic technique retains its place.

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1 Absalom AR, Marinelli G, Scott NB Spinal cord injury caused by direct damage by local anaesthesia infiltration needle. *Br J Anaesth* 2001; **87**: 512–15

2 Association of Anaesthetists of Great Britain and Ireland. *Information and Consent for Anaesthesia.* London: Association of Anaesthetists of Great Britain and Ireland, 1999

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Editor—Thank you for the opportunity to respond to Dr Crowe's letter. We are pleased that she has raised the important issue of informed consent. The strict moral and religious code by which our patient lives meant that the consent process could only be conducted *via* her husband or brother. This situation, which is not covered by the Association Guidelines (Information and Consent for Anaesthesia[1]), is common among the patients in the hospital where she was treated.

The Association Guidelines avoid the use of the term 'Informed consent', and instead distinguish between a doctor's duty to obtain consent and the duty to inform the patient of material risks. The material risks were carefully explained to the patient, *via* an experienced interpreter, on the ward before any sedatives were administered. To the best of our knowledge, she understood these risks and voluntarily consented to the procedure. She gave express (oral) consent *via* the interpreter and her husband—her husband did not provide consent on her behalf—and by coooperating with the anaesthetist before and during the procedure, she provided implied consent.

In our multi-cultured institution, we attempt to provide patient-centred health care, and put the interests of the patient first. Our role was to provide this patient with what we believed to be the best available medical care. It would have been inappropriate to question her religious beliefs, or even worse, penalize her for them.

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N B Scott
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1 Association of Anaesthetists of Great Britain and Ireland. *Information and Consent for Anaesthesia.* London: Association of Anaesthetists of Great Britain and Ireland, 1999

Is it safe to artificially ventilate a paralysed patient through a laryngeal mask?

Editor—I would like to point out yet another advantage of using the LMA† not mentioned in the editorial published in this journal.[1]

I use the reinforced LMA routinely in my paediatric practice for adenotonsillectomies and have found it to be reliable, safe, and associated with little or no coughing upon removal following awakening from anaesthesia. The hidden benefit is, in fact, the main concern of most anaesthetists unaccustomed to using an LMA for adenotonsillectomy, namely that of airway contamination with blood. It has been shown that not only does the LMA protect the airway from contamination with blood during adenotonsillectomy,[2–5] but that tracheal intubation is associated with significantly higher rates of contamination in prospective, randomized studies.[2 3] Better tolerance during emergence, with less airway obstruction (compared to a Guedel airway following tracheal extubation),[2] and less coughing and laryngospasm[3] during LMA removal make for a less eventful recovery phase, perhaps with favourable effects on the incidence of postoperative bleeding. Much larger trials would be necessary to determine the effect on bleeding, given its low incidence of 1–3% in experienced hands.

K. Lalwani
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1 Sidaras G, Hunter JM. Is it safe to artificially ventilate a paralysed patient through a laryngeal mask? The jury is still out. *Br J Anaesth* 2001, **86**: 749–53

2 Williams PJ, Bailey PM Comparison of the reinforced laryngeal mask airway and tracheal intubation for adenotonsillectomy *Br J Anaesth* 1993; **70**· 30–3

3 Boisson-Bertrand D. Amygdalectomies et masque laryngé renforcé. *Can J Anaesth* 1995; **42**: 857–61

4 Webster AC, Morley-Forster PK, Dain S, *et al.* Anaesthesia for adenotonsillectomy: a comparison between tracheal intubation and the armoured laryngeal mask airway *Can J Anaesth* 1993; **40**· 1171–7

5 Sanchez Gomez S, Garcia Iriarte MT, Abrante Jimenez A, *et al.* Laryngeal mask anesthesia technique in adenoidectomy procedures with or without tonsillectomy. *Acta Otorrinolaringol Esp* 1998; **49**. 389–96

Editor—Thank you for the opportunity to reply to the letter of Dr Lalwani who rightly noticed that I did not mention the use of the LMA for adenotonsillectomies or other ENT procedures.

In surgical procedures where the airway is shared with the surgeon (ENT and dental) there is the potential for problems. Quinn and colleagues[1] stated that the reinforced LMA provided satisfactory conditions for this type of surgery, but vigilance over the airway was required, especially at the time of dental extraction. Webster and colleagues[2] compared tracheal intubation and the armoured laryngeal mask airway for adenotonsillectomy. They showed that, after opening the Boyle-Davis gag, airway obstruction occurred in 10 patients (18.2%) in the LMA group and in three patients (6%) in the tracheal tube group. In five patients (9%), the LMA was abandoned in favour of tracheal intubation.

Use of the LMA for tonsillectomy is popular with some anaesthetists in Great Britain. However, in the light of new variant Creutzfeld-Jakob Disease in England, the Health Ministry has advised the introduction of single use surgical instruments to avoid contamination with prions and the possibility of cross infection.[3] I think that anaesthesia will have to follow the surgical direction and employ single use airway instrumentation in these cases. The cost of a single use LMA would be prohibitive unless a cheaper disposable type becomes available.

G Sidaras
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3 Risk Assessment for Transmission of vCJD via Surgical Instruments: A Modelling Approach and Numerical Scenarios Department of Health, March 2001.

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†LMA® is the property of Intavent Limited

Thoughts on the channel size of the motor endplate acetylcholine receptor

Editor—Anaesthesia textbooks, chapters and monographs on neuromuscular pharmacology often present artistic diagrams of the acetylcholine receptor (AchR) of the motor endplate. Accuracy of the diagram is of obvious importance to neuromuscular pharmacology. The size of the ionic channel determines the passage of the cations that generate the endplate potential. The topology of the channel at the receptive sites affects how muscle relaxants work.

The endplate AchR channel is generally conceived as a funnel. The extracellular portion is a cone; the membrane-crossing portion is a tube. When the channel is closed, the tube is impermeable. When the channel is open, the tube passes Na^+, K^+ and other cations as large as tetraethylammonium (TEA) and Tris, but nothing much larger. Based on the permeability of TEA, Tris, and other cations, the cross-sectional diameter of the open tube is quoted as 7.4 Å.[1] Decamethonium (C10) has two methonium heads. A methonium cation measures 5.2 Å in one direction and 6.0 Å in another. As a result, C10 can pass the channel to end up intracellularly.

Of greater interest to neuromuscular pharmacology is the dimension of the cone at the level of the two receptive sites where the relaxant molecule binds to the receptor. The inner border of the receptive sites has been estimated to be 30 Å apart in the nicotinic AchR of the electric organ.[2] Based on the optimal neuromuscular-blocking potency of muscle relaxants, Lee has proposed that, at one point of drug-receptor interaction, the space actually available to neuromuscular blocking agents measures about 20 Å.[3] It seems reasonable to assume that the helical arrangement of the amino acid residues lining the channel, their variable side chains, and the possible existence of intervening water molecules may account for the unavailability of the 10 Å (5 Å on each side).[1,3] Other explanations are possible.[1 3]

On further thought, if TEA will pass through the tube, it must first descend through the cone between the receptive sites. The passage happens when the channel is open; namely, when the two molecules of acetylcholine occupy 12 Å (6 Å for each methonium head) of the inter-site length. Subtracting from 20 Å, 8 Å remains, just enough room for passage of TEA through this portion of the cone.

It is commonly said that the cone formation of the channel increases its cross-sectional area to facilitate convergent entrance of the cations down the tube. This notion needs be qualified at the level of the receptive sites. Unless the bound acetylcholine molecules sink into the wall, they will protrude into the lumen. From the above calculation, the cone formation adds just enough room to accommodate the acetylcholine molecules, so that the remaining free space between the receptive sites is not narrower than the diameter of the open channel below. In other words, the cone formation prevents formation of an inter-site bottleneck to TEA. Additionally, it permits passage of smaller cations (Na^+, K^+) on both sides of the inter-site line. Sinking of the bound acetylcholine molecules into the wall would require large conformational change of the receptor. It would not be an energy-efficient way to provide a stable anchor or hinge for the channel to swing open below, nor would it be conducive to easy return of the acetylcholine molecules to the extracellular fluid. Little is known whether the inter-site distance increases or whether the cone itself expands when the channel opens below. Neither appears essential or economical.

This view of the AchR endplate sythesizes three key measurements: the lumen of the open tube,[4] the inter-site distance as deduced from the optimal molecular length of C10 congeners, and some other muscle relaxants,[3] and the size of the methonium head of acetylcholine, two molecules of which are required to open one nicotinic acetylcholine receptor channel.[5]

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Pulse oximetry, carbon monoxide and protective ventilatory strategies in severe ARDS

Editor—In patients with acute respiratory distress syndrome (ARDS), the use of lower tidal volumes attempts to limit ventilator-induced lung injury.[1] Positive end expiratory pressure (PEEP) has been employed to decrease the inspired fractional concentration of oxygen necessary to ensure adequate oxygenation while minimizing potential oxygen-related lung damage. The goal for the partial pressure of oxygen in arterial blood (Pa_{O_2}) is between 7.33 and 10.66 kPa.[1] This corresponds to an oxygen saturation of greater than, or equal to, 88%.

The enzyme haem oxygenase, which is the rate-limiting step in endogenous carbon monoxide (CO) production, may be induced by inflammatory stimuli, and CO has been shown to be generated in the lungs of patients who are critically ill.[2 3] In addition, CO may be produced by haemolysis in patients undergoing dialysis,[4] a common event in critically ill patients. Conventional pulse oximetry cannot differentiate between oxyhaemoglobin and carboxyhaemoglobin, and the pulse oximeter reading may be falsely elevated in the presence of carboxyhaemoglobin, leading to an overestimate of the Pa_{O_2} as compared with measurements made by laboratory blood gas analysis. This is especially important in CO poisoning.[5] Furthermore, the presence of CO causes a leftward shift of the dissociation curve of the remaining oxyhaemoglobin, partly mediated by a reduction in 2,3-diphosphoglycerate levels, leading to decreased tissue oxygenation.[6]

Recently at our institution, a 38-year-old man who had undergone peripheral blood stem cell transplantation for relapsed acute lymphocytic leukaemia, developed respiratory failure which progressed to ARDS. In addition, acute renal failure necessitated the use of continuous veno-venous haemodiafiltration. Mechanical ventilation was employed using pressure assist-control mode with an inverse I:E ratio and high levels of PEEP, while he was sedated and paralyzed. The patient had required an inspired oxygen concentration of as much as 100% to ensure a Pa_{O_2} of greater than 7.33 kPa, but this had subsequently been decreased to an Fi_{O_2} of 0.8.

As is common practice, rather than performing an excessive number of arterial blood gas analyses, the bedside pulse oximeter reading was used to titrate down the Fi_{O_2} further, aiming to keep the Sp_{O_2} at least 88%. In this patient, it was repeatedly found that the pulse oximeter haemoglobin oxygen saturation was higher than that measured by a laboratory co-oximeter, typically a discrepancy of 4–5%. For example, when the Sp_{O_2} was 88%, the measured Sa_{O_2} was 84% and the Pa_{O_2} was an unacceptably low 6.27 kPa. The measured carboxyhaemoglobin was 4%, which accounted for the artificially high Sp_{O_2} and the low Pa_{O_2}. There was no evidence for exogenous contamination with CO. A difference between pulse-oximater and co-oximeter haemoglobin oxygen saturation of 3–5% would have little, if any, clinical significance in patients with healthy lungs, or even with moderately severe lung disease. However, in patients with ARDS who have poor arterial oxygen saturation, there may be significant clinical implications, including tissue-level hypoxia.

When mechanically ventilating patients with ARDS and basing the inspired oxygen concentration on pulse oximetry, one must ensure that the pulse oximeter reading is not being artificially elevated by the production of CO in the lungs. If this is found to be the case, pulse oximetry may still be used as a guide to Pa_{O_2}, but the minimum acceptable bedside Sp_{O_2} needs to be higher.

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Failed intubation due to posterior fossa haematoma requiring emergency percutaneous tracheostomy

Editor—Percutaneous tracheostomy is a simple procedure that is routinely used in the intensive care unit.[1] We report a case of failed intubation due to a posterior fossa haematoma which required emergency percutaneous tracheostomy.

A 32-year-old female was admitted to our hospital for resection of a posterior fossa mass. Except for rheumatoid arthritis with minimal deformity, her medical history, physical examination and laboratory evaluation were normal. The laryngeal view, according to the Cormack and Lehane classification, was Grade II (glottis partly exposed, anterior commissure not seen).[2] Tracheal intubation with a size 8.0 cuffed tube was easily performed. The posterior fossa mass was excised. The patient was taken to the intensive care unit still intubated. Four hours later, she was extubated. But after 19 h, it was necessary to reintubate the patient because of a deteriorating level of consciousness and a decerebrate posture. She was also unresponsive to a painful stimulus. Although she was given fentanyl $4\,\mu g\,kg^{-1}$ and vecuronium $0.1\,mg\,kg^{-1}$, intubation was not possible due to limited cervical extension. The laryngoscopic appearance was now Grade III (only epiglottis seen). Assisted ventilation was easy using a facemask. Further intubation attempts were made with the fiberoptic bronchoscope but were also unsuccessful. In order to secure the airway, it was decided to perform a percutaneous

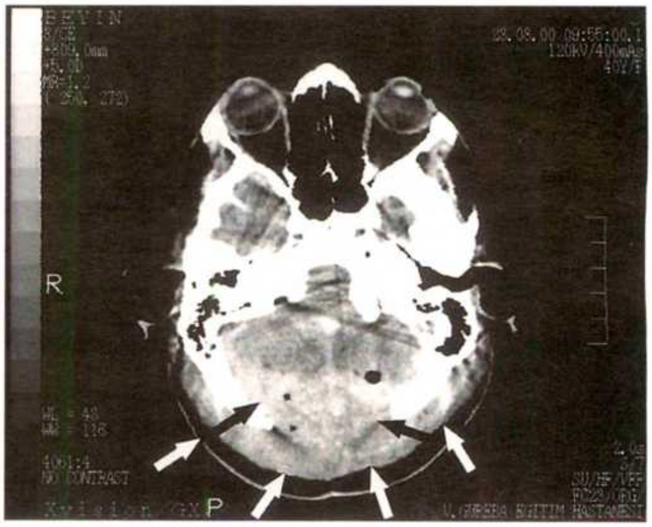

Fig. 1 CT showing a lesion 4×3 cm in diameter in occipital region (black arrows) that caused cerebellar shift and skin swelling (white arrows).

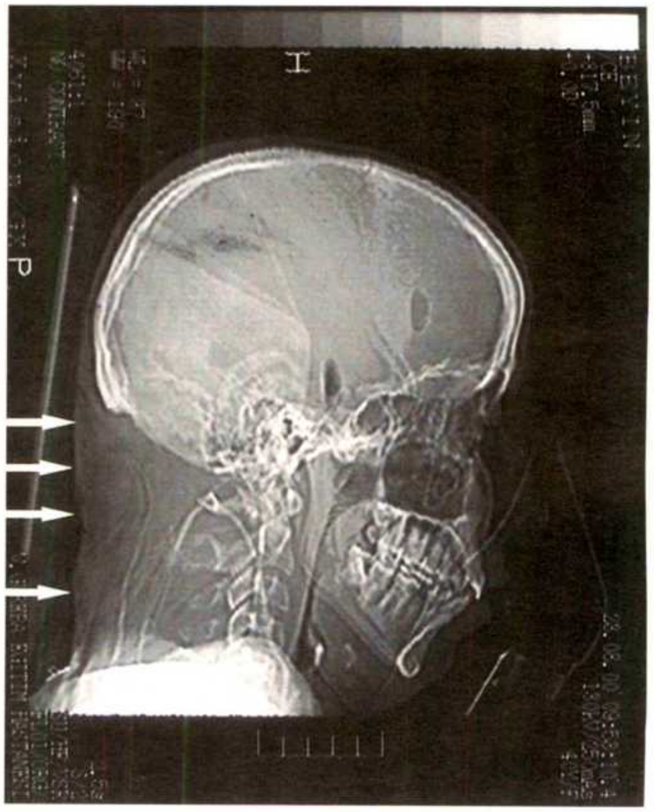

Fig. 2 Lateral CT showing swelling of the soft tissue of the neck (arrows).

tracheostomy. This was effected within 3 min, by the Griggs method, without complication. Radiological examination was then performed. Computerized tomography (CT) showed a lesion 4×3 cm in diameter in the occipital region that was causing both cerebellar shift and swelling of the skin (Fig. 1). Lateral CT showed swelling of the soft tissue of the neck (Fig. 2). It was thought to be a posterior fossa haematoma (10×3 cm in diameter) which required surgical drainage. There were no complications during the second operation or postoperatively.

There are many pathologies associated with difficulty in laryngoscopy or intubation, including tumours of the airway, malformation of the face, cervical spondylosis with limitation of neck movements, occipito-atlanto-axial disease, acromegaly and long-term diabetes mellitus with stiff joint syndrome.[3]

In this case of failed intubation from inadequate cervical extension due to a large postoperative posterior fossa/occipito-cervical haematoma, emergency percutaneous tracheostomy was life-saving. A large postoperative occipito-cervical/posterior fossa haematoma is not well documented as a cause of failed intubation, especially when intubation had earlier been achieved with ease.

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1 Anon JM, Gomez V, Escuela MP, *et al.* Percutaneous tracheostomy: comparison of Ciaglia and Griggs techniques. *Crit Care* 2000; **4**: 124–8
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British Journal of Anaesthesia **88 (2)**: 312–13 (2002)

Book Reviews

Percutaneous Central Venous and Arterial Catheterisation, 3rd Edn. I.P. Latto, W.G. Ng, P.L. Jones and B.J. Jenkins. Published by W.B. Saunders, London. Pp. 388; indexed; illustrated. Price £45. ISBN 07020 25097.

The practice of vascular access is a major part of anaesthesia with huge numbers of procedures performed in operating theatres and ICUs. Anaesthetists also increasingly provide vascular access for oncology and other specialties. In the last few years, there have been many technological improvements in devices and techniques. However, at the same time, issues in relation to complications from such procedures have been highlighted. There have been a number of well publicized medicolegal cases against anaesthetists and other specialties culminating in manslaughter charges. The release of the 3rd edition of this book is, therefore, timely.

This book follows previous editions in 1981 and 1992, and presents a comprehensive review of most aspects of vascular access. It is, as far as I am aware, the only definitive text which solely covers this subject. Despite this, I have in the past had difficulty obtaining previous editions of the book in both departmental and hospital libraries, and it has not been as widely available as I feel it deserved.

The new edition has expanded areas in relation to catheter-related sepsis, arterial catheterization and ultrasound guided vascular access. The text provides a wealth of useful information on both adult and paediatric catheterization. It is an exhaustive source of reference for all the different indications and techniques for vascular access. Individually described techniques for all the routes of vascular access are particularly useful for the interested reader. In addition, there is a very comprehensive account of all the different complications of venous access. The depth and breadth of the book in these areas can save the interested clinician hours of searching for obscure references in relation to individual techniques and complications.

I could find little overall to seriously criticize in this text; I wonder if perhaps there should be chapters sections on anatomy, imaging and longer-term venous access. Teaching of anatomy is changing. There are a wide number of anatomical web sites now available through the internet which are well worth visting. These could be referenced as well as some CDs that specifically cover vascular access. There are also many excellent new anatomical texts based on MRI, CT and cross-sectional imaging, comparing this with cadaveric cross-sections.

The imaging section could include a pictorial guide to techniques commonly used during central venous access (i.e. fluoroscopy, the post-procedure chest x-ray, the use of i.v. contrast, and the use of ultrasound guidance). There are a large number of images that practitioners rarely see but would nevertheless ideally be able to recognize and interpret in terms of catheter position and common complications. I think these should be in this definitive source book. Clinical, CT and MRI images of catheter placement, although out of the immediate area of most practitioners, nevertheless provide many useful learning points in relation to applied anatomy.

Procedures for longer-term access are increasingly provided by anaesthetists and other specialties. Although the actual insertion techniques are little different to short term access devices, and are covered in the book, there are many other aspects not covered, for example, tunnelling techniques, Dacron cuffs, port insertions, surgical techniques for catheter removal, and the place of thromboprophylaxis.

The book is generally divided into vascular access in relation to adults and children. As a result of this apparently natural division, there is quite a lot of repetition, particularly in relation to complications. Some areas of interest are more comprehensively covered in, for example, the paediatric section rather than the adult, and *vice versa*. For instance, I looked up the descriptions of so-called 'pinch off' where catheters become compressed or damaged between the clavicle and first rib. There is virtually no mention of this in the adult section, but a nice description of the problem in the paediatric section. In additon, 'pinch off' is poorly referenced in the index. Since many of the complications and other areas of interest are identical in both adults and paediatrics, it might perhaps have been better to combine some of these sections, for clarity, space and ease of use.

Overall, I have no hesitation in recommending this book to anaesthetists, surgeons, physicians and others. It is by far and away the best book I have come across in this area and should be more widely available than it has been previously. It should be available in every departmental and hospital library as a reference source for interested staff. Practitioners with an interest in the area will probably want their own copy.

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Conducting Research in Anaesthesia and Intensive Care Medicine. A.M. Zbinden and D. Thomson (editors). Published by Butterworth-Heinemann, Oxford. Pp. 550; indexed; illustrated. Price £45. ISBN 07506 4544X.

This book is essentially in two sections. The first 12 chapters deal with the process of research, from reading the literature through funding, trial design and analysis, finishing with how to deal with peer review. The second section, chapters 14 to 20, deals with techniques and research tools. The editors have selected their authors carefully. In most chapters a practical, pragmatic approach is used and the authors write with an authority born of personal experience.

There are some major highlights in the book. The third chapter is a beautifully written piece on research funding, with a very realistic, down-to-earth approach. Chapters eight and 10, both written by senior journal editors, contain fascinating insights into the process by which a manuscript is accepted for publication, as well as sage advice on how to maximize the chance of acceptance. The chapter on speaking (presenting results) is an excellent short guide to speaking, body language, and audio-visual aids. The chapter on volunteer studies gives practical advice on a research method that is rarely covered elsewhere.

Some of the information in the book is detailed and specific. In chapter nine (text processing), there are excellent tips on how to format text for equations, and how to generate automatic list numbers, chapter numbers and the like using Microsoft Word 2000. The models in chapter 17 on pharmacolgy are given for Excel spreadsheets. There are URLs for all major web resources discussed, and in some chapters supplier's details are given. Whilst these are all useful resources, they will make the book date very quickly and this might possibly detract from the more general advice and information found elsewhere in the book, which may have a longer life span.

The 'technique' chapters are a little disappointing in places. They are sometimes highly technical, and often fail to find the

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balance between being an educational article and being a technical manual. Chapter 17 progresses from one to the other, and finishes with a 296 citation reference list.

This book is primarily about research in anaesthesia. Although the title suggests that it covers intensive care research, this is really only covered in the general chapters. There is little in this book that is specific to the field of intensive care medicine. In the first section intensivists might have liked more coverage of major concerns in ICU research, such as consent and the incompetent adult. The second section on techniques does not mention anything about assays of endogenous compounds (mediators etc.), mRNA analysis, or any of the techniques used in observational/laboratory studies. In general, with the exception of chapter 20 (gene expression), the techniques section is not very forward looking.

My advice? Buy the book for yourself or your library, read and enjoy the general chapters, but get your highly detailed information on techniques from other sources.

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Non-invasive Respiratory Support. A Practical Handbook. 2nd Edn. A.K. Simonds (editor). Published by Arnold, London. Pp. 304; indexed; illustrated. Price £29.99. ISBN 0340 762594.

The appearance of the second edition of *Non-invasive Respiratory Support* is timely because, under the remit of the Modernisation Agency, there is likely to be a drive towards the provision of non-invasive respiratory support services within all acute hospitals, with an estimated requirement of four such beds per 250 000 million population. This is both to relieve pressure on intensive care beds and because of documented improved short-term outcomes within certain groups of conditions, such as acute respiratory failure in chronic obstructive pulmonary disease and in the immunocompromised, as compared with invasive ventilatory assistance. To this end, the book contains guidelines for the extablishment of a non-invasive respiratory support service, with good sections on the role of nurses and physiotherapists. The unstated assumption is that the medical care would be led by the respiratory physician team, but the practicalities of this in smaller hospitals are not addressed. This is of direct relevance to intensivists involved in intensive and high dependency care and, indeed, there will undoubtedly be further discussion of the location of such a service which can draw from within these pages. The need for a rolling education programme for staff is emphasized several times.

Dr Anita Simonds has skilfully maintained a coherent text of just under 300 pages by authoring or co-authoring 13 of the chapters, whilst the remaining seven chapters are contributed to by other UK or European physicians, or nursing or physiotherapy professionals. The contents page does not include the page number whereby the chapter may be quickly located although the chapter heading does appear at the top of every left hand page. Each chapter starts with a summary of the section headings, and references are generous, totalling 800, and up-to-date. None of the chapters is over long, despite the inevitably complex detail in reviewing the existing evidence, and they are generously illustrated with useful tables, illustrations, guidelines etc. A couple of appendices list useful resources by their UK address, telephone and web sites where available.

There are a few errors: the time- and flow-cycling waveforms on page 91 are transposed, and the last reference on page 254 has been omitted. I would have liked to see a more detailed exposition of CPAP machines in the chapter dealing with equipment, and a mention of the pressure limitation facility on some volume ventilators which allows them to function as robust pressure limiting machines.

Starting with a good historial overview, the book ends with Dr Branthwaite's ethical and medico-legal summary of aspects of assisted ventilation in the UK. The remainder of the chapters may be grouped into the role of non-invasive respiratory support in the acute situation, its role in the domiciliary setting, and summarizing the current international consensus on the subject. There are useful chapters devoted to technical and practical aspects, and a chapter recounts the delivery of respiratory support in Europe and the USA.

Anaesthetists will have much to learn from this comprehensive, state-of-the-art summary which includes discussions on respiratory insufficiency in pregnancy, in children, in the scanning department, in the dental surgery, and in obstructive sleep apnoea. World-wide, non-invasive continuous positive pressure airway therapy is being prescribed increasingly on a long-term basis for obstructive sleep apnoea, and increasing numbers of patients are having non-invasive positive pressure ventilation in the home for a range of restrictive conditions. Anaesthetists are increasingly likely to be faced with surgical patients who are having some form of long-term non-invasive respiratory support and will need to be well informed to manage the perioperative phase appropriately. Whether in the respiratory unit, intensive care unit or the anaesthetic office this book ought to be allocated a place on the shelf.

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ABSTRACTS

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*(The name of the author presenting the paper is shown in bold type. *Indicates non-member. All authors have certified that, where appropriate, studies have been conducted with the approval of the relevant Human Ethics Committee or Animal Experimental Review Committee)*

VERBAL PRESENTATIONS

Comparison of methods of administration of high frequency jet ventilation in a model of laryngotracheal stenosis

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High frequency jet ventilation (HFJV) is frequently used during anaesthesia for patients with laryngotracheal stenosis.[1] Two main problems are potential for barotrauma and an inability to monitor non-invasively the adequacy of ventilation. HFJV can be administered by three methods: supraglottic, subglottic using a catheter placed through the tracheal stenosis (translaryngeal), and subglottic using a cannula placed through the wall of the trachea (transtracheal). The aim was to investigate which method is associated with the least potential for barotrauma by measurement of end expiratory pressure (EEP) in the airway of a bench-top model.

A Monsoon Universal Jet Ventilator, set at an inspiratory time of 30%, delivering 100% oxygen (O_2) at 2 bar and a rate of 150 breaths min^{-1}, was connected to a tracheal-lung model comprising a hollow tube (internal diameter 22 mm) connected to a 2-litre bag. To simulate tracheal stenosis, connectors of fixed internal diameters (2.5–8.5 mm) were attached to the proximal end of the hollow tube. Supraglottic HFJV was delivered 1 cm proximal to the connector, whilst translaryngeal and transtracheal HFJV were delivered 4 cm below the connector. EEP was measured from within the hollow tube. The results show that supraglottic HFJV is associated with significantly higher EEP than translaryngeal and transtracheal HFJV (Figure 1).

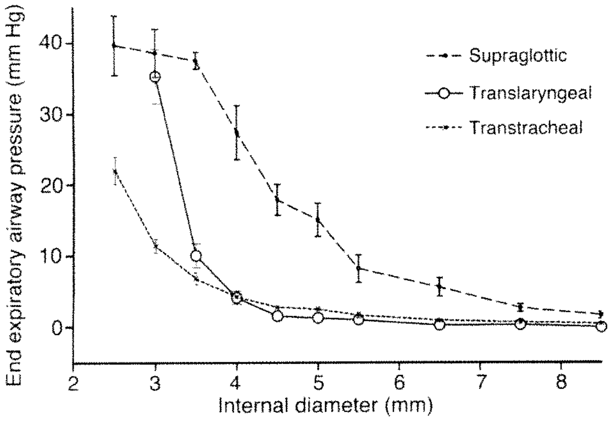

Fig 1 EEP expressed as mean (95% CI).

In a second experiment, we simulated the degree of ventilation and air entrainment by sampling gas from within the 2-litre bag during the three methods of HFJV delivered with connectors of internal diameters 3.5–7.5 mm attached to the proximal end of the hollow tube. Nitrous oxide (N_2O) 4 litre min^{-1} was administered to the system through the hollow tube during HFJV. N_2O and O_2 were measured. N_2O concentrations were lower and calculated nitrogen concentrations were higher for supraglottic HFJV than translaryngeal and transtracheal HFJV. The higher EEP associated with supraglottic HFJV may be attributable to increased ventilation and increased air entrainment, compared with the two subglottic methods.

Keywords: ventilation, high frequency; complications, tracheal stenosis

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An examination of the association between predicted postoperative FEV_1 and cardiac and respiratory complications in patients undergoing pneumonectomy

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Many patients presenting for lung resection have a reduced respiratory reserve. A recent review highlighted predicted postoperative FEV_1 ($ppoFEV_1$) as a useful predictor of postoperative complications in patients undergoing lung resection.[1] The use of $ppoFEV_1$ is supported by some authors, but has been found by others to be of limited value.[2 3] In the study described here we examined the associations in our own surgical population between $ppoFEV_1$ and postoperative complications in patients undergoing pneumonectomy.

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Table 1 Predicted postoperative FEV$_1$ values in patients who did and did not suffer postoperative complications

	Cardiac complications		**Respiratory complications**		**Cardiac or respiratory complications**	
	No	**Yes**	**No**	**Yes**	**No**	**Yes**
ppoFEV$_1$						
Absolute value (litres)						
Mean (SD)	1.1 (0.33)	1.1 (0.24)	1.1 (0.34)	1.0 (0.18)	1.1 (0.35)	1.0 (0.21)
ppoFEV$_1$						
Percentage of predicted						
Mean (SD)	38.6 (11.4)	42.4 (11.4)	40.1 (11.7)	34.2 (8.8)	39.7 (11.7)	37.7 (11.0)

The patient database maintained by the Bristol Cardiothoracic Unit was used to identify patients who underwent pneumonectomy between September 1998 and March 2000. Fifty-five patients were identified. The notes of these patients were obtained and data were recorded on the age and sex of the patient, on the operation performed, and on respiratory and cardiac complications occurring in the first 30 days after surgery. Ten patients suffered postoperative respiratory complications and nine suffered postoperative cardiac complications. Overall, 16 patients suffered a postoperative cardiac or respiratory complication. Using the method described by Kearney and colleagues,[2] the predicted ppoFEV$_1$ was calculated both as an absolute value and as a percentage of the predicted value for a healthy subject. The ppoFEV$_1$ values for patients who suffered complications and for those who did not are shown in Table 1.

Using the Wilcoxon rank sum test, the ppoFEV$_1$ values were compared in patients who suffered postoperative complications and those who did not. No significant differences were found. Our data do not support a clinically useful association between ppoFEV$_1$ and postoperative complications in patients undergoing pneumonectomy.

Keywords: surgery, lung resection; complications

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Mathematical modelling of oxygen balance defines theoretical hypoperfusion limits for cardiopulmonary bypass

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It was previously shown by continuous arteriovenous oximetry that marked increases in oxygen consumption occur following acute reductions in bypass flow rate. Following short periods of flow reduction, oxygen recovered during flow restoration may be double the calculated oxygen debt.[1]

Flow reduction at surgical request, to reduce capillary bleeding, is carried out by perfusionists and currently regulated in an arbitrary manner. There is no pre-defined safe period of flow reduction,[2] no agreement on bypass flow rate reduction and no consideration of a safe interval between flow down periods at a given temperature, haematocrit and metabolic rate.

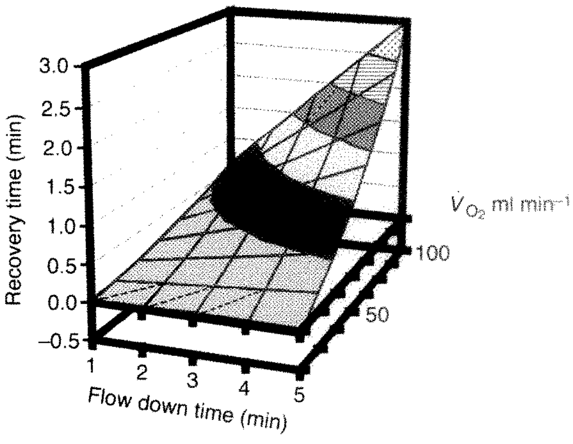

Fig 2 Modelled inter relationship of oxygen consumption, flow down and recovery time.

Assuming oxygen requirements remain constant, and oxygen debt during flow down must be repaid upon flow restoration, a simple linear model interrelating oxygen delivery, oxygen consumption and recovery from oxygen debt may be defined (Figure 2).

Where: $\mathbf{OER_1}$, $\mathbf{OER_2}$, and $\mathbf{OER_3}$ are basal, flow down, and recovery oxygen extraction ratios, $\mathbf{D_1O_2}$, $\mathbf{D_2O_2}$, and $\mathbf{D_3O_2}$ are basal, flow down and recovery oxygen deliveries, $\mathbf{T_{fd}}$ is the flow down period.

$$\text{Recovery time} = T_{fd} \text{x} \frac{[(\text{OER}_1 \times \text{D}_1\text{O}_2)] - (\text{OER}_2 \times \text{D}_2\text{O}_2)]}{[(\text{OER}_3 \times \text{D}_3\text{O}_2)] - (\text{OER}_1 \times \text{D}_1\text{O}_2)]}$$

Calculations from continuous arteriovenous oximetry may be of value in determining safe flow rate reduction intervals in terms of a patient's actual metabolic demands, and offers a potential improvement over current practice.

Keywords: surgery, cardiopulmonary bypass; models, oxygen consumption

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The effect of tetrodotoxin on the cilia beat frequency of human inferior turbinate tissue

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The mucociliary escalator is an important protective mechanism of the respiratory tract, of which the continued beating of cilia is an integral part. Previous studies have demonstrated that commonly used local anaesthetics, including lidocaine and cocaine, reduce ciliary beat frequency (CBF)[1] but the mechanism remains unclear. This study was undertaken to investigate whether the slowing of CBF associated with local anaesthetics could be attributed to the action of these drugs as sodium channel inhibitors. Ciliated turbinate epithelial samples were exposed to a pure sodium channel inhibitor, the marine toxin tetrodotoxin (TTX), an extremely potent polar local anaesthetic that is the poison of a variety of Japanese puffer fish (*Spheroides spengleri*).[2]

Samples of inferior turbinate tissue from eight patients were washed with a modified 199 medium containing added glutamine, penicillin, streptomycin, fungizone and 10% fetal calf serum before discs were obtained using a punch biopsy. An existing and previously presented transmitted light technique[1] was used to record a resting CBF in HEPES buffered Hanks solution at a pH 7.4 and temperature of 37°C. The discs were then exposed to a 100 mM TTX solution prepared according to the manufacturer's instructions and controlled for pH and temperature and the CBF recorded at regular time intervals thereafter.

The results are presented in Table 2. These data suggest that the CBF of nasal cilia were unaffected by the sodium channel inhibitor, tetrodotoxin.

Table 2 Mean CBF (Hz) (with 95% CI) before and after application of TTX

Pre TTX	1 min	5 min	10 min	30 min	60 min
14.13 (12.6–15.7)	14.60 (13.9–15.4)	14.17 (13.0–15.3)	14.42 (13.1–15.7)	14.40 (12.9–15.9)	14.67 (13.3–16.0)

Keywords: respiratory tract, cilia; anaesthetics local, tetrodotoxin

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Laryngoscopy conditions in spontaneously breathing patients: an incremental step-up regimen using propofol by target controlled infusion

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Inhalational induction of anaesthesia using halothane or sevoflurane has traditionally been the method of choice for attaining adequate depth of anaesthesia in those patients where it is imperative to maintain spontaneous respiration.[1] However, a significant proportion of patients find inhalational induction unpleasant, even with sevoflurane.[2] The increasing use of Target Controlled Infusion (TCI) systems has provided the ability to control the rate of induction and depth of anaesthesia using propofol.[3] The purpose of this interventional study was to induce anaesthesia in incremental steps to determine the stage at which satisfactory conditions for laryngoscopy could be achieved in spontaneously breathing patients, using propofol TCI.

We studied 31 ASA I or II patients undergoing elective surgery. Patients known or predicted to be difficult intubations (modified Mallampati score 3 or 4) or with a history of gastric reflux were excluded. Intravenous access was established and baseline measurements of heart rate (HR), blood pressure (MAP), and oxygen saturation (Sp_{O_2}) were recorded at the start and at 1-min intervals thereafter. Capnography confirmed spontaneous respiration throughout. After preoxygenation, propofol TCI was commenced at $1\ \mu g\ ml^{-1}$ and the target was increased by $0.5\ \mu g\ ml^{-1}$ every 30 s until anaesthesia was induced as assessed by loss of verbal contact and eyelash reflex. Laryngoscopy was attempted 1 min after loss of consciousness and intubating conditions assessed using a standard scoring system based on jaw relaxation, exposure/position of vocal cords, coughing, and limb movement (graded 1–4). The target level was increased by $0.5\ \mu g\ ml^{-1}$ if conditions were deemed unfavourable (any score ≥ 3) and further laryngoscopy attempted 1 min later. This pattern was followed until successful laryngoscopy was achieved (all scores ≤ 2).

Over half (17/31) had favourable laryngoscopy conditions on the 1st attempt, and almost 90% (27/31) by two further increments after loss of consciousness, that is on the 3rd attempt (Table 3). Unsuccessful laryngoscopy was most commonly due to moderate limb movement (16/27 total failures), with the rest split between stiff jaw and coughing (5/27 and 6/27). There was a decrease in MAP after induction and post laryngoscopy (statistically but not clinically significant) but no difference in HR. Sp_{O_2} did not fall below 95% at any stage and there were no episodes of apnoea. No patient had any recall of instrumentation. All rated the technique as pleasant and would be willing to undergo the same again.

Keywords: anaesthetic techniques, laryngoscopy, direct; anaesthetics i.v., propofol

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Table 3 Outcome of laryngoscopy in 31 patients receiving propofol TCI step-up regimen. Values are number or median (range)

	1st attempt	2nd attempt	3rd attempt	4th attempt	5th attempt
Number of patients	31	14	8	4	1
Successful	17	6	4	3	1
Propofol target ($\mu g\ ml^{-1}$)	5.5 (4–8)	5.75 (5–6.5)	7.0 (4.5–7.5)	6.0 (6–7.5)	6.0

Hyperacute liver failure: what threshold for raised intracranial pressure should we accept?

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Raised intracranial pressure (ICP) is a well-recognized feature of hyperacute liver failure, and is thought to occur in around 70% of cases. The potential for survival despite very high intracranial pressure in liver failure has been reported.[1] Is there a critical value for ICP, or a critically low value for cerebral perfusion pressure (CPP), associated with non-survival?

We studied 106 consecutive cases of hyperacute liver failure resulting from paracetamol poisoning. All patients developed grade 3–4 encephalopathy, and were intubated, ventilated and underwent invasive haemodynamic monitoring including intracranial pressure monitoring. We recorded peak ICP and the number of hours the ICP exceeded 20, 25, 30 Torr, respectively. Likewise, minimum CPP and the number of hours CPP was below 60, 50, 40 and 30 Torr were recorded. We also documented noradrenaline requirement, lowest pH and highest prothrombin time These variables were compared with outcome (survival), and those significantly related to survival were entered into a logistic regression model to assess which were independently correlated with survival. To analyse this further, we measured glial cell fragment S100 in a subgroup of 13 patients over their ICU stay.

Sixty-five patients died and 41 survived. All survivors were grossly neurologically intact. The only variables independently correlated with survival were pH (odds ratio 319 per pH unit, 95% CI 5.5–5.7×10^9) and duration (h) below a CPP of 40 Torr (odds ratio 0.1, 95% CI 0.014–0.66). Mean pH in survivors was 7.28 (7.24–7.31) *vs* 7.18 (7.15–7.22) in non-survivors. Duration with a CPP below 40 Torr was 1.17 h (0–3.1) in survivors, *vs* 2.6 (1.2–4) in non-survivors. We were unable to find any relationship between S100 and survival or between S100 and duration of raised ICP or reduced CPP.

In conclusion, our results show that acidosis and a cerebral perfusion pressure below 40 are associated with reduced survival in paracetamol poisoning. S100 may not be a useful surrogate marker in this patient population. Further studies are required to establish whether ICP and CPP changes in liver failure are related to neurological damage or are merely a marker of the severity of circulatory failure.

Keywords: liver, acute failure, brain, intracranial pressure

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In vitro estimation of cerebral critical closing pressure during simulation of intracranial hypertension

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Pathological increase of intracranial pressure (ICP) causes progressive collapse of vulnerable beds of the intracranial vasculature and eventually brain ischaemia. The arterial pressure at which collapse occurs and flow becomes zero is the critical closing pressure (CCP).[1] This measurement is of paramount importance, but not always feasible in the clinical setting. Recently, a method of estimating zero flow pressure in a circulatory simulator using Doppler ultrasonography demonstrated 100% sensitivity in reflecting changes of perfusion pressure.[2] We aim to evaluate if the same method can reflect changes of CCP occurring as a result of step increases of intracranial pressure in a simulator of cerebral circulation

Table 4 Changes in CCP

Change in pressure surrounding collapsible tube	Mean of the change of CCP (mm Hg)	95% confidence intervals (mm Hg)
0–6 cm H_2O (*n*=8)	4 89	1.51–8.26
6–12 cm H_2O (*n*=8)	8.31	5.71–10 91
12–18 cm H_2O (*n*=8)	6 96	2 41–11 52
18–24 cm H_2O (*n*=8)	7 44	5 26–9 62

An *in vitro* pulsatile flow model was constructed using artificial vessels and perfusion media. A section of the vasculature was modified to include a collapsible area. The flow velocity profile in the carotid artery was simulated and measured using an 8 MHz Doppler probe at a fixed angle. The driving pressure (DP) and downstream pressure were transduced. Changes in ICP were simulated by increasing the level of water in a vessel surrounding the collapsible tube. Eight configurations were used combining a range of driving pressure, downstream pressure and resistance characteristics. At each configuration we performed five sets of measurements of flow velocity and driving pressure, at 0, 6, 12, 18 and 24 cm H_2O. The CCP was calculated as.

$$CCP = DP_{mean} - (DP_{mean} - DP_{diastolic}) \times FV_{mean}/(FV_{mean} - FV_{diastolic})^{3}$$

At 0 cm H_2O the CCP calculated for eight different configurations ranged from 4.57 to –16 38 mm Hg. Each step change of 6 cm H_2O changed the CCP in a predictable direction in 30 out of 32 changes (sensitivity 94%). The mean and confidence intervals of the changes of CCP at each step are given in Table 4.

The overall difference between the absolute change in surrounding pressure and the estimated change in CCP was 2.5 mm Hg (95% confidence intervals 1.06 to 3.93 mm Hg) (*n*=32).

In this bench test we have shown that Doppler ultrasonography is a sensitive and useful tool for detecting changes in CCP produced by 6 cm H_2O or more change in the simulated ICP

Keywords: models, critical closing pressure; measurement techniques, Doppler ultrasonography

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Effects of 50% nitrous oxide on estimated cerebral perfusion pressure and zero flow pressure in healthy volunteers

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Recently, non-invasive methods of estimating cerebral perfusion pressure and zero flow pressure (ZFP) using transcranial Doppler ultrasonography (TCD) have been described[1] It has been suggested that ZFP should be taken as the effective downstream

Table 5 Effect of N_2O on BP, $P\text{E}'_{CO_2}$, FV_{mean}, eCPP and ZFP. Median (interquartile range)

	Baseline	50% N_2O	Kruskal–Wallis
BP_{mean} (mm Hg)	83.83 (75.75–89.25)	86.00 (81.83–106.08)	P=0.318
$P\text{E}'_{CO_2}$ (kPa)	5.50 (+5.2 to +5.6)	5.45 (+5.2 to +6.05)	P=0.557
FV_{mean} (cm^{-1})	63.00 (+58.75 to +66.00)	89.00 (+78.00 to +96.5)	P=0.024
eCPP (mm Hg)	67.02 (+42.5 to +78.9)	99.9 (+87.9 to +114.6)	P=0.009
ZFP (mm Hg)	25.45 (−0.28 to +34.73)	−9.65 (−17.2 to −1.1)	P=0.006

pressure in the calculation of cerebral perfusion pressure.[2] Nitrous oxide is a known cerebral vasodilator. We aimed to study the effect of nitrous oxide on the estimated cerebral perfusion pressure (eCPP) and ZFP as assessed by TCD.

We studied eight healthy volunteers. Subjects were supine and continuous measurements of middle cerebral artery (MCA) blood flow velocity (FV) were made using a 2 MHz transcranial Doppler ultrasound probe. Blood pressure (BP) was measured non-invasively using a Dinamap, and end-tidal carbon dioxide ($P\text{E}'_{CO_2}$) measured using a facemask and capnograph. After baseline measurements subjects were asked to breathe 50% nitrous oxide through an anaesthetic breathing circuit until inspired and expired nitrous oxide concentrations equilibrated. Repeat measurements of MCA FV and BP were then taken

The following formulae were used to calculate the eCPP and ZFP.

$$eCPP = [FV_{mean} / (FV_{mean} - FV_{diastolic})] \times [BP_{mean} - BP_{diastolic}]$$
$$ZFP = BP_{mean} - eCPP$$

Nitrous oxide significantly increased FV_{mean} and eCPP and consequently decreased ZFP (Table 5). This may imply that nitrous oxide significantly decreases cerebral arteriolar tone, which is suggested to be a major determinant of ZFP.

Keywords. measurement techniques, transcranial Doppler ultrasonography; brain, cerebral perfusion pressure

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Propofol blood levels, clinical sedation scores and electrophysiological variables in children emerging from propofol infusion anaesthesia

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Effecting optimum sedation of the critically ill child remains a difficult issue in PICU. Large inter-patient variability in drug requirements leads to periods of over and under sedation.[1] Clinical management relies on crude observations using pain and discomfort scores.[2] Derived measures of cortical EEG may be a potentially useful tool in children. We have therefore examined the correlation of EEG, blood propofol levels, and sedation score during a stepwise emergence from propofol sedation in PICU.

We studied 10 children aged 5 months to 8 yr after non-complex open heart surgery. Post-surgical sedation overnight was with fentanyl (10 μg kg^{-1} h^{-1}) and propofol. For 2 h prior to the study all patients remained on 4 mg kg^{-1} h^{-1} propofol in order to achieve a steady state. Propofol infusions were decreased in a step-wise fashion from 4 mg kg^{-1} h^{-1} in 1 mg kg^{-1} h^{-1} steps at 30 min intervals until arousal EEG recording and serial blood propofol levels were made from deep sleep to the time of arousal. Clinical sedation scores using the COMFORT scale were given at each steady state.[2]

While there was some increase in COMFORT scores with decreasing propofol levels, COMFORT scores had little value in predicting the point of arousal. The measured COMFORT scores changed almost instantaneously from over sedated to awake (under sedated). The inter-patient blood propofol concentrations varied widely at the highest infusion rate (mean=1853.2 ng ml^{-1}, SD=382.8) and also at the point of arousal (mean=1086.4 ng ml^{-1}, SD=310.4).

We found the best EEG variable to be the summation of the following three ratios: β/δ1, β/δ2, β/θ. (β/θ=13–32 Hz, θ=5–8 Hz, δ1=0.5–2 Hz, δ2=2–5 Hz) The equation describing the regression of this EEG variable with blood levels was·

$$y=1134\times^{0.2304}$$

with a R^2 of 0.64;

and with propofol infusion rates was:

$$y=0.6564\times^{1.7288}$$

(R^2=0.47).

This EEG variable also discriminated between the deeply sedated group (highest infusion rate) and the same group in the 5 min prior to waking (P=0.00002) However, the correlation of the EEG variable with sedation score was not significant.

These results highlight the poor correlation of COMFORT score with blood propofol levels, and its difficulty in predicting the point of arousal. Monitoring of sedation score in this group of patients, on infused propofol, will not prevent sudden and uncontrollable emergence However, changes in power of cortical EEG at high to low frequencies was related to propofol infusion rate, propofol concentration and emergence and therefore has potential to be developed as a predictive tool.

Keywords: anaesthetics i.v., propofol; monitoring, electroencephalography

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Postoperative wound tissue oxygen tension with epidural or intravenous analgesia

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Postoperative wound infection may be a serious complication of surgery. Adequate wound tissue oxygen tension (Pw_{O_2}), which is decreased by postoperative pain, is essential for wound healing.[1 2]

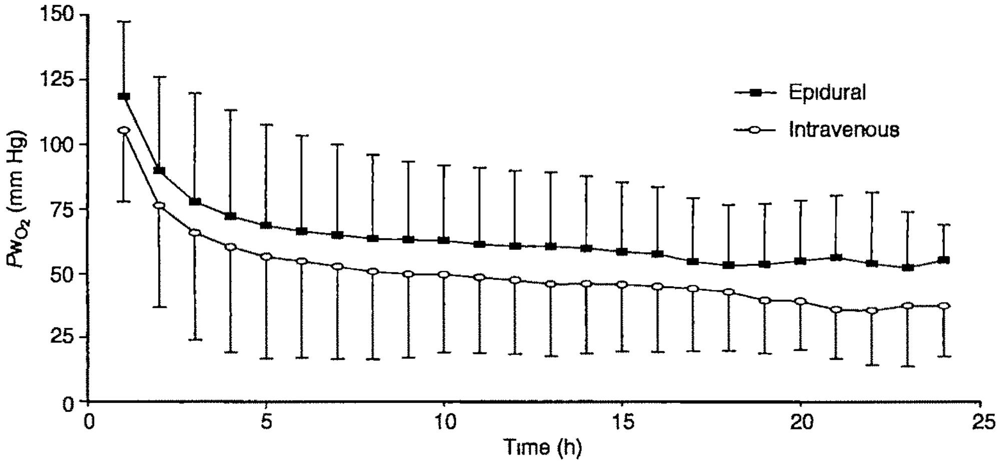

Fig 3 Pw_{O_2} values over 24 h Values are mean±SD.

We hypothesized that epidural anaesthesia and analgesia would increase Pw_{O_2} compared with standard general anaesthesia and i.v. morphine by providing superior pain relief.

In a prospective, randomized, blind trial, 32 patients undergoing major abdominal surgery received either combined general and epidural anaesthesia with postoperative patient-controlled epidural analgesia (Epi), or general anaesthesia alone with postoperative patient-controlled i.v. analgesia (IV). An oxygen electrode (Licox Medical Systems™) and a temperature sensor were placed subcutaneously in the longitudinal axis of the wound before final surgical closure. Direct wound oxygen tension (Pw_{O_2}) and temperature were measured continuously for 24 h and the data downloaded to a laptop PC. Other variables affecting wound tissue oxygenation and visual analogue scale (VAS) pain scores were also recorded.

Although Epi patients were colder at the end of surgery (35.7 (0.3) *vs* 36.3 (0.5)°C, P=0.004), they had significantly greater mean Pw_{O_2} over the 24 h period, compared with the IV group (64.4 (14) *vs* 50.7 (15) mm Hg, mean (SD), 95% CI difference, −22 to −5, P=0.002, see Figure 3). VAS pain scores at rest and on moving were significantly less in the Epi group at all times. Wound temperature exceeded core temperature in both groups postoperatively, but did not differ between groups. We conclude that combined with general anaesthesia, epidural anaesthesia and postoperative analgesia for major abdominal surgery increased Pw_{O_2} over 24 h compared with standard general anaesthesia and i.v. morphine analgesia, suggesting that it may have a role in reducing postoperative surgical-wound infection.

Acknowledgement: This study was funded by a grant from University Hospitals of Leicester.

Keywords: pain, postoperative; analgesia

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Effects of plasma from septic patients on the vascular reactivity of omental blood vessels isolated from patients undergoing routine abdominal surgery

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Sepsis is known to affect vascular tone and reactivity. The mechanisms involved in humans are poorly understood as the majority of research in this field has been conducted in animals Our aim was to study (*in vitro*) the effect of plasma from septic patients on the vascular reactivity of omental vessels isolated from patients undergoing routine abdominal surgery.

On the intensive care unit, a 5 ml blood sample was collected from each of 10 patients, who fulfilled the criteria for severe sepsis.[1] The blood sample from each septic patient was paired with an age/sex matched blood sample from a non-septic patient (ASA I or II undergoing elective surgery). After collection into a lithium heparin bottle, each sample was centrifuged, and the plasma was divided into 0.2 ml aliquots. The plasma pairs were coded and stored in a freezer at −80°C and were thawed immediately prior to use. Omental biopsies were obtained from 12 female ASA I and II patients, who were scheduled for routine abdominal surgery. The omental biopsy was placed immediately into physiological salt solution (PSS) at 4°C and an investigator isolated an artery by microscopic dissection. The fresh omental artery (radius 0.109–0.225 mm) was divided into three sections. Each vessel section was incubated either with 2% plasma from septic patients, 2% plasma from non-septic patients (matched) or PSS with heparin (control) for 18 h at 4°C. Following incubation, each vessel was mounted on a multichannel Mulvany-Halpern wire myograph,[2] heated to 37°C, and normalized to the diameter at which the greatest active tension was attained. Vessels were subjected to constriction with five incremental doses of vasopressin (1×10^{-10} to 1×10^{-8} M), until maximum steady-state constriction was achieved. The vessels were then relaxed with serial doses of bradykinin (1×10^{-10} to 3.3×10^{-6} M). The force generated by the vessel was recorded on a paper chart recorder and analysed by a blinded investigator. Maximal intravascular

Table 6 Effect of sepsis on V_{max}

	V_{max} (mm Hg)		Kruskal–Wallis
	Median	Interquartile range	
Septic plasma	90	61–114	P<0 024
Non-septic plasma	128	105–146	
PSS and heparin	124	114–137	

pressures (V_{max}) were calculated using an established method, utilizing the Law of Laplace. If the pressure generated in the control vessel was less than 60 mm Hg, the experiment was discarded.

Two experiments were discarded due to poor control vessel contraction In seven out of 10 experiments, the maximum pressure in the vessels treated with plasma from septic patients was impaired, resulting in a significant decrease in V_{max} (Table 6).

Acknowledgement: We thank the Association of Anaesthetists of Great Britain and Ireland for the project grant.

Keywords: arteries, vascular reactivity; infection, sepsis

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Microdialysis under hyperbaric conditions

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Microdialysis is a technique for collecting interstitial substances *in vivo*.[1] Equipment produced by CMA/*MicrodialysisAB* is CE labelled for use in human adipose tissue and skeletal muscle. The system uses a flow of 0.3 µl min^{-1} through the dialysis catheters. We performed *in vitro* tests confirming that the pump functioned as expected under hyperbaric conditions,[2] then we planned to study changes in glucose, lactate and pyruvate under ischaemic conditions and the effect of hyperbaric oxygen during the reperfusion period. We observed an interesting phenomenon with large variations in the volume of dialysate collected during changes in environmental pressure.

A CMA 60 microdialysis probe was inserted into both thighs of volunteers. 0.9% saline was pumped through the probes using a CMA 106 pump. Dialysate was collected for three 30-min periods prior to inflation of a tourniquet placed on the upper thigh of one leg for 40 min. After 90 min the tourniquet was re-inflated for 40 min, at the end of which the volunteer breathed 100% oxygen at 2.8 ATA. The pressure was maintained at this level for 60 min and then returned to normal gradually over 30 min. Dialysate was collected throughout.

As pressure increased, the volume of dialysate greatly decreased (Table 7). During the decompression phase, the volume increased markedly to volumes greater than that being supplied by the pump. During initial *in vitro* tests, there was no change in the pump flow so any loss or gain of dialysate must be due to external influences. This phenomenon has not been previously described and further investigation is needed of the effects of environmental pressure on fluid homeostasis.

Table 7 Volume of dialysate (µl) collected during each 30-min time period (4&8 = 40 min tourniquet inflation)

	LEG	1	2	3	4	5	6	7	8	9	10	11
A	control	6	8	6	8	8	6	4	0	0	0	12
	study	8	6	8	8	6	6	6	4	0	0	14
B	control	6	8	8	8	6	6	8	0	4	6	8
	study	6	8	8	12	6	6	8	10	0	2	12
C	control	6	8	8	10	6	8	6	0	4	4	16
	study	8	8	8	10	4	6	6	0	0	4	12
Total		40	46	46	56	36	38	38	14	8	16	74

Acknowledgement: We wish to thank the staff of NWERU for their co-operation and help with this study.

Keywords. measurement techniques, microdialysis, hyperbaria, hyperbaric chamber

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Impact of different volume replacement solutions on the formation of platelet microvesicles in porcine septic shock

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Sepsis and septic shock are associated with a relative and an absolute intravascular volume deficit and with an activation of the clotting system. Platelet activation in sepsis leads to an increased formation of microvesicles,[1] which are platelet derived membrane vesicles with procoagulant activity.[2] The formation of microvesicles has been associated with increased mortality in endotoxaemic pigs [3] The aim of our study was to investigate a possible impact of different volume replacement solutions on microvesicle formation in a porcine model of septic shock.

Fasted, anaesthetized, mechanically ventilated and multi-catheterized pigs (20.9 (1.9) kg) received 1 g kg^{-1} body weight faeces into the abdominal cavity to induce sepsis and were observed over 8 h. At induction animals were allocated randomly to resuscitation with modified fluid gelatin 8% (MFG8%) (*n*=5), modified fluid gelatin 4% (MFG4%) (*n*=5), 6% HES 200/0.5 (*n*=5), or Ringer's solution (RS) (*n*=5). Infusion rate was titrated to maintain a central venous pressure of 12 mm Hg. Before induction of sepsis (baseline) and after 2 (+2 h), 4 (+4 h), and 8 (+8 h) h citrated blood samples were taken. Flow cytometry was used for determination of microvesicles. Platelets and microvesicles were identified with an anti-platelet-mAb (Donor: D.H. Sachs, Charlestown, USA) and a secondary antibody labelled with phycoerythrin (goat-anti-mouse, Dako SA, Denmark). Microvesicles were determined as the smallest 1–3% positive cells in forward scatter. Data are presented as mean (SD). Statistical intergroup comparison was performed using Wilks-Lambda and Ryan-Einot-Gabriel-Welsh-F-test. $P<0.05$ was considered significant.

Baseline values were considered as 100%. In the RS-group sepsis was associated with an increase of microvesicles to 137 (58)% after 2 h, leading to 179 (45)% (+4 h) up to 210 (121)% (+8 h). In group HES there was an increase at +2 h (109 (25)%) and a decrease at +4 h (89 (26)%) and +8 h (73 (19)%). In the MFG4% and MFG8% groups a decrease in microvesicles after induction was revealed at +2 h (51 (25)%, MFG4% and 45 (16)%, MFG8%) +4 h (62 (10)%, MFG4%, 79 (58)%, MFG8%) and +8 h (63 (41)%, MFG4%, 53 (17)% MFG8%). Eight h after the induction of sepsis, the formation of microvesicles was significantly higher in the RS group compared to group HES, MFG4% and MFG8%.

In this porcine model of septic shock, the formation of platelet derived microvesicles was increased by Ringer's solution and decreased by colloids.

Table 8 Median (range) PID scores in patients receiving 2.5–7.5 mg CBME

	15 min	30 min	45 min	1 h	1.5 h	2 h
2.5 mg (rest)	12 (+3 to +34)	–4 (–33 to +34)	14 (+5 to +22)	10 (–5 to +17)	7 (–12 to +13)	0 (–23 to +19)
2.5 mg (movement)	25 (+10 to +35)	18 (–5 to +44)	25 (+14 to +35)	35 (+4 to +52)	11 (–1 to +39)	0 (–19 to +44)
5 mg (rest)	13 (–1 to +28)	18 (+17 to +36)	17 (0 to +41)	25 (–4 to +58)	11 (0 to +32)	0 (0 to +35)
5 mg (movement)	29 (–17 to +36)	31 (–1 to +37)	16 (–7 to +43)	24 (–16 to +62)	20 (0 to +46)	0 (0 to +22)
7.5 mg (rest)	19 (–4 to +49)	32 (+4 to +55)	24 (+2 to +43)	22 (+2 to +44)	23 (+4 to +48)	0 (–24 to +44)
7.5 mg (movement)	27 (–7 to +53)	35 (+3 to +63)	32 (+7 to +69)	34 (+3 to +58)	18 (+7 to +44)	5 (–3 to +11)

Keywords: blood, platelets, microvesicles; fluids, i.v.

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An open-labelled, dose-finding study of the analgesic and side-effects of a cannabis-based medicine extract in a model of postoperative pain

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There is considerable interest in the potential use of cannabinoids for pain relief.[1] The effect of a standardized cannabis-based medicine extract (CBME) on postoperative pain has not been investigated. We report the first administration of a sublingual spray of CBME (Delta-9-tetrahydrocannabinol) in patients with pain after total abdominal hysterectomy.

Anaesthesia was standardized and immediate postoperative pain relief provided by patient-controlled analgesia (morphine 1 mg bolus, 5 min lock-out). The PCA was discontinued on the morning after surgery. When the patient requested analgesia, CBME was administered sublingually. Four patients were studied at each dose: 2.5 mg, 5 mg, and 7.5 mg, starting at 2.5 mg. Patients receiving larger doses were only recruited if the previous group reported no significant adverse events. Patients were observed at 15-min intervals for 1 h then at 1.5, 2, 3, 4, 5 and 6 h. Rescue analgesia was available at all times. Visual analogue scores for pain (rest and on movement), sedation scores, vital signs, adverse events (including feelings of well-being, increased awareness of surroundings, dry mouth, palpitations, difficulty with memory and co-ordination, change of mood, slurring of speech, blurred vision, confusion and dizziness), time to rescue analgesia and overall satisfaction were measured. Adverse events, sedation scores and vital signs were also monitored at 8 and 24 h.

Table 8 shows median (range) VAS pain intensity difference (PID) scores up to 2 h. In individual patients, this was set to zero if escape analgesia was given (three of four patients in each group received by 3 h).

All patients reported pain relief on global assessment (two slight, five good, five very good) Median (range) time to rescue analgesia was 140 (95–305), 108 (85–275), 150 (140–265) min at 2.5 mg, 5 mg, 7.5 mg, respectively. Three patients experienced mild nausea and vomiting following administration but there were no other adverse events Only one patient would not use the medication again for pain relief.

Clinically significant pain relief was demonstrated in several patients with no significant adverse events but there was no comparison with placebo. However, these data facilitate the design of larger placebo-controlled studies on the use of CBME in the postoperative period.

Keywords: ataractics, cannabinoids; analgesia

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A prospective patient-specific cost analysis of alternative anaesthetic regimens in adult day-case surgery

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The aim of this study was to compare the costs of four anaesthetic regimens in adult day surgery: total i.v. anaesthesia (TIVA) with propofol; propofol induction, isoflurane/N_2O maintenance, pro-

Table 9 Length of stay and principal cost parameters *F (3, 1059) 175.56, P=0.0001. Significant differences detected between all groups except between propofol/isoflurane and sevoflurane/sevoflurane

Mean (SD)	Propofol/propofol (*n*=265)	Propofol/isoflurane (*n*=267)	Propofol/sevoflurane (*n*=280)	Sevoflurane/sevoflurane (*n*=251)	*P*
Length of stay (h)	8.9 (10.9)	9.3 (11.4)	8.8 (10.9)	9.3 (11.8)	n.s
Total NHS cost (£)	125.6 (79.9)	119.7 (85.1)	121.0 (83.9)	124.1 (95.4)	n.s
Anaesthetic cost (£)	11.3 (6.4)	4.8 (2.3)	7.1 (2.2)	4.7 (2.3)	0.0001*
Patients' own costs (£)	0.12 (0.41) *n*=228	0.10 (0.41) *n*=232	0.08 (0.32) *n*=235	0.13 (0.51) *n*=212	n.s

pofol induction, sevoflurane/N_2O maintenance; sevoflurane/N_2O induction, sevoflurane/N_2O maintenance.

A total of 1063 unpremedicated adults, aged 17–87 yr undergoing day-case gynaecology, general or orthopaedic surgery were allocated randomly to one of the four alternatives. Cost data collected for the period of admission were: fixed costs, staff time, all drug and disposable equipment use, and adverse event management. Patient-specific data were collected prospectively. Quantity of volatile anaesthetic agent use was determined using Dion's approximation.[1] Post-hospital resource use data were collected during a telephone interview with the patient 7 days post-discharge Unit costs for the year 2000 were attached to resource use. Statistical analysis using SAS™ 6.12 was carried out using ANOVA (1% level to account for multi-group comparisons).

Anaesthetic drug costs constituted between 4% and 9% of total costs (Table 9). Propofol/isoflurane and sevoflurane/sevoflurane were statistically significantly lower in cost than propofol/sevoflurane, and TIVA with propofol was higher in cost than all other groups. There were extremely low post-discharge costs to both NHS and the patient, demonstrating that day-case discharge policies were clinically appropriate.

Although the anaesthetic drug costs were different for the four groups in this study, this difference had no impact on overall costs. This indicates that increases in anaesthetic costs were offset by reductions in the use and costs of other health care services, or absorbed by the variation in other costs.

Acknowledgement: Funded by the National Co-ordinating Centre for Health Technology Assessment (UK).

Keywords: surgery, day-case; anaesthesia, audit, costs

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A prospective patient-specific cost analysis of propofol and halothane *vs* sevoflurane in paediatric day-case surgery

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Newer anaesthetic agents are perceived to be more costly and anaesthetists are increasingly required to incorporate cost into their decisions around drug choices. The aim of this study was to compare the costs of a propofol induction and halothane/N_2O maintenance, with a sevoflurane/N_2O induction and maintenance technique.

Table 10 Length of stay and principal cost parameters. *n=125, **n=135 Propofol costs are based on that used

Mean (SD)	Propofol/ halothane (n=159)	sevoflurane/ sevoflurane (n=163)	P
Length of stay (h)	5.2 (2.4)	5.1 (1.9)	n.s.
Total NHS cost (£)	84.1 (21.4)	86.8 (22.1)	n.s.
Anaesthetic drug cost (£)	1.9 (0.8)	3.0 (1.3)	0.0001
Parents' own costs (£)	0.04 (0.26)*	0.03 (0.18)**	n.s.

A total of 322 unpremedicated children, aged 3–13 yr undergoing day-case general or ENT surgery were allocated randomly either to receive propofol (with lidocaine) induction with halothane/N_2O-maintenance, or sevoflurane/N_2O induction and maintenance. Cost data collected for the period of admission were: fixed costs, staff time, all drug and disposable equipment use, and adverse event management. Patient-specific data were collected prospectively The quantity of volatile anaesthetic agent use was determined using the Dion approximation.[1] Post-hospital resource use data were collected during a telephone interview with the patient's parent or guardian 7 days post-discharge. Unit costs for the year 2000 were attached to resource use. Statistical analysis using SAS™6.12 was carried out with unpaired Student's t tests.

Anaesthetic drug costs constituted between 2% and 3% of total costs (Table 10). The children who had propofol/halothane incurred significantly lower anaesthetic drug costs than those who had sevoflurane/sevoflurane. There were extremely low post-discharge costs to both NHS and the parent, demonstrating that day-case discharge policies were clinically appropriate.

Previous studies show that the cost of drugs is a small proportion of the total anaesthetic cost, as low at 4% in day surgery and sometimes less than 1% in inpatient surgery.[2] Although the anaesthetic drug costs were different for the two groups in this study, this difference had no impact on overall costs. The results of this study indicate that focusing on drug costs may not reduce overall anaesthesia costs significantly and that organizational and operational factors require equal levels of investigation.

Acknowledgement: Funded by the National Co-ordinating Centre for Health Technology Assessment (UK).

Keywords: surgery, day-case, paediatric; anaesthesia, audit, costs

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Morphine glucuronides inhibit $DiOC_2$ excretion from human lymphocytes

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P-glycoprotein (P-gp) is an ATP-dependent efflux protein present in many human cell types. It transports both drugs and physiological substrates.[1] In malignant cells, P-gp expression has been associated with the onset of resistance to chemotherapeutic agents, and inhibitors of P-gp may restore chemosensitivity[2] Many commonly used drugs interact with P-gp. We undertook a pilot study investigating the influence of clinically relevant concentrations of morphine, morphine-3-glucuronide (m-3-g), and morphine-6-glucuronide (m-6-g) on the extrusion of the P-gp substrate $DiOC_2$, a fluorescent dye, from human lymphocytes obtained from six healthy volunteers. Lymphocytes express P-gp[3]

Blood samples (50 ml) were obtained. Lymphocytes were separated by density gradient centrifugation using Histopaque™ and then incubated with 500 nmol litre^{-1} morphine, 5000 nmol litre^{-1} m-3-g or 1000 nmol litre^{-1} m-6-

g before loading with dye. The rate of dye extrusion from the lymphocytes was assessed by diminution in $DiOC_2$-associated fluorescence at 1, 2 and 3 h as measured by flow cytometry. Comparisons were made with a control population of lymphocytes from the same volunteer that were not incubated with opioid before dye loading. The percentage fall from maximum fluorescence was measured and the difference of the fall between control and opioid-loaded cells calculated. The median differences at 1, 2 and 3 h were assessed and 94% confidence intervals calculated employing the Wilcoxon Signed Rank Test. The calculations were performed using the computer software package Minitab™ v10.5xtra for Macintosh. Results are shown in Table 11.

Table 11 The median difference (94% CI, $n = 6$) of the dye-associated fluorescence between study and control cell populations. Data normalized to 100% (baseline) and refer to *less* extrusion; $^*P<0.05$

Time (h)	morphine (500 nmol litre^{-1})	m-3-g (5000 nmol litre^{-1})	m-6-g (1000 nmol litre^{-1})
1	–2 (–8.3 to +8.4)	+12.6* (+0.9 to +39.9)	+14.5* (+9.8 to +19.6)
2	–6.6 (–4.4 to +10.4)	+9.8 (–1.1 to +19.3)	+7.5 (–5.5 to +12.4)
3	–3.5 (–7.8 to +32.2)	+14.9* (+0.6 to +37.5)	+9.8* (+6.1 to +29.5)

There was a decrease in dye extrusion from lymphocytes incubated with m-3-g and m-6-g when compared with controls. This may be due to inhibition of P-gp by these glucuronides. Morphine was not associated with a reduction in the rate of dye extrusion.

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Keywords: protein, P-glycoprotein; metabolism, morphine

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Membrane-bound TNFα: a biologically relevant cytokine?

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The role of tumour necrosis factor α (TNFα) in inflammatory states, including sepsis, has been well described.[1] Such studies concentrated on soluble TNFα (solTNF), a circulating product formed from cleavage of membrane-bound TNFα (memTNF) by a membrane metalloproteinase (TNF cleaving enzyme, TACE).[2] In animal models, when TACE activity is blocked (allowing the accumulation of memTNF) there is an increased incidence of organ-specific inflammation,[3] indicating a potential pathophysiological role for memTNF. We developed a method to measure memTNF protein and bioactivity in human monocytes.

Elutriated human monocytes (1×10^6 cells) were either plated alone, stimulated with lipopolysaccharide (LPS 10 ng ml^{-1}) or stimulated with LPS in the presence of 10 μM BB94 (a protease inhibitor). At harvest (2, 4 and 24 h), monocytes were fixed with 1% paraformaldehyde and memTNF protein measured by flow cytometry (using optimized antibody combination) and bioactivity by WEHI assay. Flow cytometry data are expressed as mean fluorescence intensity (MFI) ± standard deviation from three experiments (10 000 cells in each experiment). TNF bioactivity is expressed as % cell death in WEHI cells (data representative of three experiments).

MemTNF was increased by LPS stimulation at 4 and 24 h and levels further increased by the addition of BB94 (Figure 4 left panel). The increase in memTNF positively correlated with WEHI cell death, indicating memTNF bioactivity (Figure 4 right panel). Therefore, memTNF on monocytes can be detected by flow cytometry and appears to be bioactive. This suggests that memTNF may be a biologically important form of TNFα and may be responsible, in part, for the organ-specific injury seen in TNFα-driven diseases, such as sepsis.

Acknowledgement: This work was funded by a grant from the Arthritis Research Council, UK.

Keywords: polypeptides, cytokines, tumour necrosis factor

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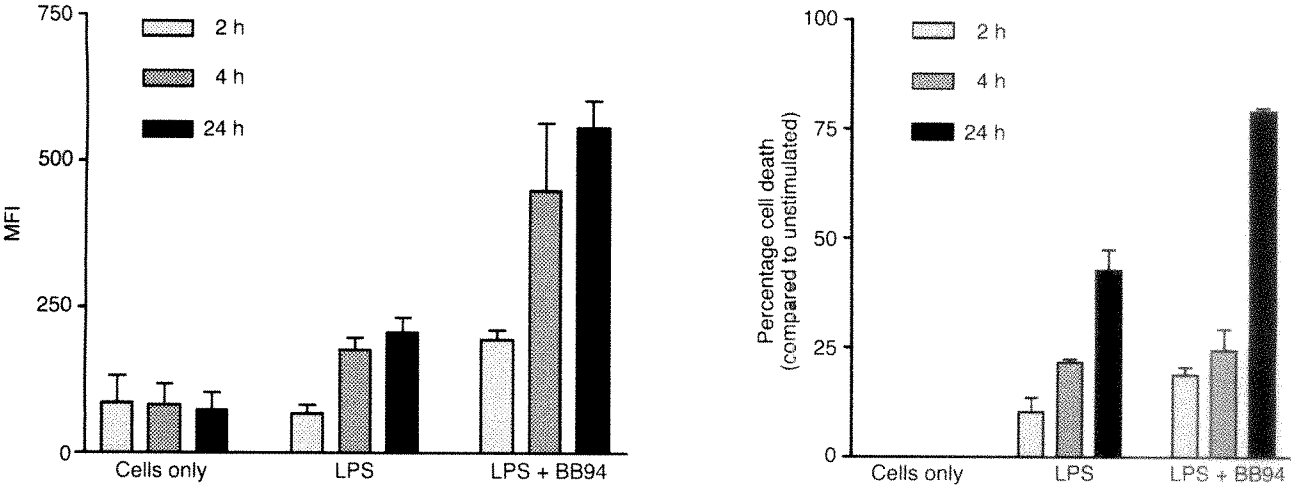

Fig 4 MemTNF protein levels (left panel) and TNF bioactivity (right panel).

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Investigating the molecular determinants of anaesthetic interaction with $\beta_1\beta_3\beta_2$ subunit containing $GABA_A$ receptors

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At clinically relevant concentrations, most i.v. general anaesthetic agents enhance the action of GABA at the inhibitory $GABA_A$ receptor.[1] Interaction of etomidate with $GABA_A$ receptors is of particular interest as it is dependent upon their subunit composition exhibiting selectivity for β_2- and β_3- compared with β_1- subunit containing receptors.[2] We have previously demonstrated that the substitution of a single amino acid within the TM 2 domain of β subunits can dramatically influence the GABA-modulatory and -mimetic effects of etomidate.[3] Here we have examined the effect of substituting asparagine 289 of the β_3 subunit with naturally occurring amino acids in an attempt to identify physiochemical properties (e.g. size, polarity, hydrophobicity) that correlate with the activity of etomidate.

Xenopus laevis oocytes were injected with cRNAs encoding wild type (WT) or mutant subunits. Two to 12 days later, inward current responses evoked by GABA were recorded under voltage clamp at a holding potential of –60 mV. To investigate the enhancement of agonist evoked responses by etomidate, a concentration of GABA producing a peak current 10% of the maximum (EC_{10}) was determined for each oocyte. Etomidate was pre-applied for 60 s before co-application with GABA. The anaesthetic E_{max} (the amplitude of the GABA-evoked response in the presence of a maximally effective concentration of anaesthetic expressed as a percentage of the maximal effect of GABA) and the EC_{50} (the concentration of anaesthetic producing half maximal enhancement) were determined. All observations are based on a minimum of three oocytes.

All mutations reduced potentiation by etomidate (0.1–300 μM) relative to the WT β_3 subunit and, in the instances of substitution by isoleucine and methionine, modulation was completely abolished. At higher anaesthetic concentrations (30–300 μM), GABA-mimetic effects were noted with WT receptors displaying direct effects amounting to 33 (3.0)% of the GABA maximal response while mutant receptors displayed a sensitivity ranging from no effect (isoleucine) to 15.7 (3.1)% (alanine). Furthermore, replacement of this crucial residue produced parallel shifts in GABA-concentration responses with isoleucine (β_{3N289I}) producing the greatest shift (13-fold decrease) in potency in comparison to WT responses. Single regression analysis did not identify any significant correlation relating the size, polarity, hydrophobicity etc. of the substituted amino acids with GABA modulatory activity suggesting that, at the receptor level, the interaction of etomidate with $\alpha_1\beta_3\gamma_2$ $GABA_A$ receptors may be influenced by more than one molecular determinant.

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Keywords: anaesthetics i.v., etomidate; receptors, $GABA_A$

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Is postoperative recovery related to preanaesthetic anxiety?

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Anxiety is commonplace prior to surgical procedures, but can this affect quality of postoperative recovery?[1 2] We have previously shown that a linear analogue anxiety score (LAAS) can be an easy and reliable assessment of preanaesthetic anxiety, compared to the anxiety questions of the Hospital Anxiety and Depression Scale HAD questionnaire.[3]

ASA I and II patients presenting for diagnostic gynaecological laparoscopy (including laparoscopic sterilization) were studied. Patients were presented with the LAAS (on an 11 point incremental score, 0–10) and HAD scale questionnaire (0–21) prior to arrival in the anaesthetic room. All patients were contacted by telephone on day 1 and day 3 and asked about mobility (0=in bed to 3=full normal activity), pain (0–3), and nausea and vomiting (0–3). Any contact with outside help such as their GP or NHS Direct was also noted. Altogether 118 patients completed the preanaesthetic scores, 108 patients were contacted postoperatively on day 1 and 85 on day 3. Data were analysed using SPSS 10.0 for Spearman correlation between LAAS and HAD and *multiple linear regression* between preanaesthetic anxiety as the dependent variable and the postoperative outcomes of mobility, pain and emesis as *determinants*. The residual variability gives the proportion of the variability of preanaesthetic stress which can be accounted for by the variability of the postoperative outcomes. Mean preanaesthetic LAAS was 3.79 (2.56), median 3.5 (range 0–10). Mean HAD score was 7.2 (4.24), median 7 (range 0–21). These values are similar to the scores we found for minor gynaecological surgery.[3] Spearman correlation between HAD and LAAS was 0.73 ($P<0.01$). There was no individual correlation between preanaesthetic anxiety and postoperative observations on either day 1 or day 3 (Table 12). Altogether, these 3 postoperative outcomes could account for only 4% on day 1 and 0.1% on day 3 of the variability of preanaesthetic stress. Two patients contacted their GP because of inadequate control of pain and a further three for surgical reasons.

From our data, we cannot show any evidence that preanaesthetic stress affects quality of postoperative recovery. Our numbers were relatively small but to show any significant effect of preanaesthetic stress on outcome would probably require very large numbers of patients.

Table 12 Mean or median postoperative scores (range)

	Day 1 (*n*=108)	**Day 3 (*n*=85)**
Pain (0–3)	2 (0–3)	1 (0–2)
Nausea/vomiting (0–3)	0 (0–2)	0 (0–1)
Mobility (0–3)	1 (0–3)	3 (2–3)
Outcome variability accounted for by pre-anaesthetic stress	3.95%	0.1%

Table 13 Randomization group characteristics

Group	Prop TIVA (*n*=265)	Sevo (*n*=251)	Prop/Iso (*n*=267)	Prop/Sevo (*n*=280)	*P*
Age, years, mean (SD)	44.7 (15.3)	43.8 (14.9)	44.3 (15.4)	43.5 (15)	n.s
Female : male ratio	2.9	3.0	2.9	2.9	n.s.
Alert in recovery (*n*)	158	140	159	163	n.s.
Drowsy in recovery (*n*)	91	87	88	101	n.s
Agitated in recovery (*n*)	15	19	21	13	n.s
Min in recovery, mean (SD)	41.1 (20.6)	42.4 (23.5)	40.4 (20.3)	41.1 (20)	n.s
Min to home discharge, mean (SD)	321 (639)	330 (699)	346 (672)	317 (650)	n.s
Number admitted (*n*)	26	24	24	26	n.s

Keywords: surgery, preanaesthetic anxiety; recovery, postoperative

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Propofol, sevoflurane and isoflurane: a comparison of early postoperative recovery in adult day-case anaesthesia

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Anaesthetic agents that enable a safe and rapid return to the community should be used in day-case surgery to minimize disruption of the patient's routine.[1] Recovery from anaesthesia should be pleasant and as free as possible from adverse events. We investigated recovery after propofol alone (TIVA), sevoflurane alone, or i.v. induction with propofol and maintenance with either sevoflurane or isoflurane in adult day-case patients.

Adults (n=1063) undergoing day-case general, gynaecological or orthopaedic surgery were allocated randomly to receive either propofol (TIVA), sevoflurane/N_2O alone, propofol with isoflurane/N_2O maintenance, or propofol with sevoflurane/N_2O maintenance. The mental state of the patient in recovery, times to discharge to the ward and from the hospital, and overnight admission rates were recorded. Statistical analysis was performed using analysis of variance and χ^2 test.

A study in paediatric patients has demonstrated that recovery after sevoflurane/N_2O anaesthesia is more rapid, albeit associated with more initial agitation than after propofol and halothane anaesthesia.[2] Some adult day-case studies have found a more rapid emergence using sevoflurane,[3] but this has not been substantiated by other workers.[4] In this larger study we found no differences in speed of recovery, quality of recovery, or overnight admission rates between the four anaesthetic techniques (Table 13). This suggests that the increased cost of more expensive agents, be they i.v. or volatile, may not be justified by recovery experience or discharge times.

Acknowledgement: This study was funded by a grant from the National Co-ordinating Centre for Health Technology Assessment (UK).

Keywords: surgery, day-case; recovery

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Analysis of 16 460 obstetric epidurals performed by consultants and trainees: is there a difference in outcome?

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The Wansbeck Epidural Audit System[1] is a computerized audit system running in six sites in the UK (Leeds General, Wansbeck General Hospital, Blackpool Victoria Hospital, Sunderland Royal Hospital, Pembury, Royal Victoria Infirmary Newcastle). Data from the six units were anonymized with respect to patient and anaesthetist identity, then pooled and analysed. The pooled database contained 18 757 records of which 16 460 were inserted by either a consultant or trainee (10% and 75% of total respectively). The aim of the current study was to compare outcome of epidurals inserted by consultants and trainees.

Delivery and follow-up data were recorded in 65% (one unit partially implemented the system and only recorded insertion and follow-up data) and 85% of consultant cases and in 79% and 85% of trainee cases respectively. Compared to trainees, consultants were more likely to insert the block in routine hours (08.00–17:00) (80% *vs* 40%; P<0.0001), after induction of labour (40% *vs* 27%; P<0.0001) and at an earlier stage of labour (<2 h) (34% v 27%: P<0.0001) (Chi-squared test). There were no differences in any outcome measure studied (Table 14). Mode of delivery (consultant *vs* trainee): SVD% (57 *vs* 56); Instrumental% (24 *vs* 25); Caesarean% (19 *vs* 18). Accidental dural puncture was recorded in 10 consultant cases (0.50%) and in 73 trainee cases (0.50%). A post-dural puncture headache was recorded in nine consultant and 98 trainee cases.

Table 14 Results shown as consultant *vs* trainee as %, *recorded by midwife as part of delivery data immediately after delivery; ** recorded by anaesthetist at follow-up visit

	Excellent	Satisfactory	Unsatisfactory	Poor
Midwife assessment*	55 *vs* 57	34 *vs* 33	7 *vs* 7	4 *vs* 3
Patient assessment**	72 *vs* 70	21 *vs* 22	5 *vs* 5	2 *vs* 3
Analgesia in labour**	77 *vs* 75	16 *vs* 18	5 *vs* 5	2 *vs* 2
Analgesia for delivery **	47 *vs* 50	28 *vs* 28	13 *vs* 14	11 *vs* 8

It is reassuring to find that the quality of an epidural performed by an anaesthetist in training is equivalent to that of a consultant. This service commitment of the training grade to the obstetric epidural service should be more widely recognized.

Keywords: analgesia, obstetric; anaesthetic technique, epidural

Reference

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A double blind dose-finding trial of clonidine in combination with 0.125% bupivacaine by infusion for postoperative epidural analgesia

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Alpha-2 adrenergic agonists provide analgesia *via* an opioid-independent mechanism. In common with opioids, they have a bupivacaine-sparing effect, but are not associated with the side-effects of opioids such as pruritus, respiratory depression, and nausea and vomiting.[1] The aim of our study was to compare the analgesic efficacy and side effect profile of two different concentrations of clonidine in 0.125% bupivacaine.

Sixty ASA I – II patients undergoing hip or knee replacement under combined general and epidural anaesthesia were studied. The hospital pharmacy allocated the patients randomly to receive one of three test solutions, and prepared and labelled the solutions. Patients, anaesthetists and nursing staff were blinded. A high lumbar epidural cannula was inserted, and 10 ml of 0.5% bupivacaine administered. Adequate block was confirmed prior to induction and maintenance of anaesthesia using target-controlled infusions of propofol and alfentanil. Thirty min later, an epidural infusion of test solution was commenced (10 ml h^{-1}). All patients received 0.125% bupivacaine. No clonidine was added to the solution used for group A, whereas groups B and C received clonidine 0.6 $\mu g\,ml^{-1}$ and 1.2 $\mu g\,ml^{-1}$ respectively both at 10 ml h^{-1}. Postoperatively, ward staff recorded pain (observer-assessed and VAS), sedation and motor power scores, and epidural block height, respiratory rate, NIBP and heart rate 4-hourly for 24 h. If analgesia was inadequate up to two top-ups of 0.25% bupivacaine 5 ml were given before the infusion rate was increased. NSAIDs or morphine were also given as required. Statistical analysis was performed using ANOVA, Kruskal–Wallis, Mann–Whitney or Fisher's Exact tests, as appropriate.

Groups were similar for age, weight, duration and type of surgery, and initial block height. Mean heart rate and arterial blood pressure, and minimum Sp_{O_2} and respiratory rate were similar for the three groups throughout the study period. VAS pain scores, and observer-assessed pain, sedation and motor power scores were similar for the three groups (Table 15). The requirements for epidural top-ups and rescue analgesia were significantly different among the groups. While there was a trend toward a lesser requirement for top-ups and rescue analgesia in group C compared with group B, this difference was not statistically significant. We conclude that both clonidine 0.6 $\mu g\,ml^{-1}$ and clonidine 1.2 $\mu g\,ml^{-1}$ enhance the analgesia provided by 0.125% bupivacaine without causing a significant increase in adverse effects.

Table 15 VAS, pain and sedation scores, epidural top ups and supplementary analgesia requirements

Study group	VAS (mean)	Pain score (median)	Sedation score (median)	Epidural top ups (number of patients)	Supplementary analgesia (number of patients)
Group A	1.4	0.67	0	16	16
Group B	1.0	0.32	0	14	6
Group C	1.1	0.32	0	8	3
P	n.s	n.s	n.s.	0.005	0.027

Keywords: analgesia, postoperative, epidural; analgesics non-opioid, clonidine

Reference

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Intraperitoneal and incisional bupivacaine with epinephrine for analgesia following total abdominal hysterectomy

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Incisional[1] or intraperitoneal[2] local anaesthetic instillation during surgery has not been shown to produce opioid sparing effects compared with placebo. The aim of this prospective double blind randomized placebo controlled trial was to investigate if a combination of intraperitoneal and incisional bupivacaine with epinephrine would reduce morphine consumption following total abdominal hysterectomy (TAH).

We studied 46 ASA I-II patients listed for TAH *via* a Pfannenstiel incision. Exclusion criteria were malignancy, drug allergy and a chronic pain syndrome. All patients received a standardized anaesthetic of propofol 2–4 mg kg^{-1} i.v., a non-depolarizing muscle relaxant, morphine 10 mg i.v., ondansetron 4 mg i.v. and rectal paracetamol 1g. Their lungs were ventilated with nitrous oxide and isoflurane in oxygen *via* a cuffed tracheal tube. At the end of the procedure, residual neuromuscular blockade was reversed with neostigmine 2.5 mg and glycopyrrolate 500 μg. Postoperatively, patients received i.v. morphine *via* a patient controlled analgesia (PCA) device and rectal paracetamol 1g 6-hourly. Patients were allocated by computer randomization to receive 50 ml of bupivacaine 0.25% with epinephrine 5 $\mu g\,ml^{-1}$ or 50 ml of normal saline. Following instructions from sealed opaque envelopes, 30 ml and 20 ml of the treatment solution were administered into the peritoneum and incision respectively before wound closure. Postoperatively, morphine consumption was recorded hourly and assessments of pain at rest and on movement were made by a member of staff blinded to the treatment, on awakening and then at 8, 12 and 24 h.

Seventeen and 16 patients in the placebo and bupivacaine groups, respectively, completed the study. There were no significant differences between the bupivacaine and placebo groups in age, height, weight or duration of surgery. Pain on movement were significantly higher in the placebo group than in the bupivacaine group on awakening. Morphine consumption (interquartile range) over 24 h was 62 (53–85) mg in the placebo group compared with 44 (33–56) mg in the bupivacaine group (P<0.01). This significant difference was attributable to the significantly higher morphine consumption in the placebo group in the first 4 h postoperatively.

Keywords. analgesia; anaesthetics local

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A continuous competence-based assessment programme for senior house officer training in anaesthesia

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We have developed a questionnaire-based system for assessing the competence in clinical practice of Senior House Officers (SHO) training in our hospital. The system is intrinsic to everyday working practice and utilizes all 34 consultants in our department. Each trainee is assessed on every theatre list during which they are attached to a consultant, during the 6-month rotation through our department. We assessed two cohorts of seven SHO in the first 5 months, and six in the second 6 months. All had completed a minimum of 18 months of anaesthetic training. The trial was designed to assess the form's ease of use, fairness and flexibility, and estimate any increases in workload it may cause.

The questionnaire was approved for use by the North Trent Anaesthetic Training Committee and designed to appraise trainee development in the broadest way. The categories comprise: theoretical knowledge, practical ability/aptitude, clinical/diagnostic acumen, reliability/punctuality, communication skills, problem solving ability, awareness of limitations, record keeping, professional manner and general enthusiasm and interest. The questions were scored from 5 (excellent) to 1 (poor). The maximum score possible was 50. The form was unblinded, and the assessor ticked a box if they had discussed it with the trainee. It also logged whether the trainee had seen the list preoperatively, and contained a trainee 'supervision score' out of three: '1' (requires constant supervision); '2 (can practice independently within limitations); '3' (can supervise others).

Completed forms (370) were entered into the database. All 10 criteria were marked on 348 forms (94.1%). The remaining 22 forms (5.9%) had between six and nine criteria completed. Mean assessment scores for individual SHOs ranged from 35.8 to 44.1. Only three forms had scores <25, and three different forms had an individual criterion scored 1 (poor). Data took around 2 min per form to input. Mean supervision scores ranged from 2.0 to 2.7.

Consultants completed a questionnaire (shown in Table 16) at the end of each 6 months. They felt this assessment system to be convenient, easy to implement and fair. It gave detailed data on trainee performance throughout 6 months training. Data processing was rapid and simple.

Keywords: education, medical training, assessment

Table 16 Formal response to the following questions 'Regarding the form in particular, and the system in general'

	Yes (%)	**No (%)**	**Undecided (%)**
Was the form easy to use?	96	0	4
Did you require guidance on completion?	7	93	0
Was it comprehensive?	93	7	0
Did the form unduly influence your opinion?	14	86	0
Do you discuss your assessments with each SHO?	28	61	0
Is this an acceptable method of assessment?	96	4	0

Evaluation of personal, biological and environmental monitoring of paediatric anaesthetists exposed to nitrous oxide

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Chronic exposure to waste anaesthetic gases may lead to health risks, leading to recommendations restricting exposure[1] Paediatric anaesthetists' exposure to nitrous oxide (N_2O) may exceed safety limits.[2] Previous work has concentrated on environmental sampling giving an idea of pollution in the breathing zone, but not a true picture of an individual's 'dose'. Biological sampling will give us more information and some work has looked at Biological Exposure Indices.[3] COSHH recommends a time-weighted average of 100 p p.m. over 8 h. This work examines exposure of paediatric anaesthetists to N_2O assessed by environmental, personal and biological monitoring.

Twelve operating lists were targeted in three different environments. Environmental sampling tubes were attached to anaesthetists for the duration of the list. Urine and end-tidal breath samples were collected at the beginning, middle, end of lists and 1 h postoperatively. Sampling tubes were analysed by thermal desorbtion and gas chromatography. Samples from an indwelling venous cannula were taken at baseline, after each induction and 1 h postoperatively. Gas chromatography was used to analyse urine and blood samples.

The range of values is wide and some exceed exposure limits (Table 17). Breath samples taken at the end of MRI lists reflect high acute exposures as do urine and blood samples. Our MRI unit is a typical non-theatre environment, without a conventional anaesthetic room or induction scavenging. Although the sample is small, acute exposure to N_2O may be a problem in rapid turnover paediatric lists. Further work is needed to consolidate data and provide information on the cognitive effects of short-term exposure.

Acknowledgement: Work supported by a grant from The Association of Anaesthetists of Great Britain and Ireland.

Keywords: anaesthetics gases, nitrous oxide; anaesthetics gases, occupational exposure

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Table 17 Nitrous oxide levels mean (range)

	Dental unit (*n*=4)	**Day surgery (*n*=4)**	**MRI unit (*n*=4)**
Mean number of patients per list	6	6	4
Breath (p p m)	56 (22–104)	76 (<1–343)	106 (6–396)
Environmental (p p.m.)	34 (27–45)	52 (<1–132)	70 (11–188)
Urine (μg litre^{-1})	8 (0–18)	20 (0–53)	43 (0–155)
Blood (μg litre^{-1})	42 (0–154)	112 (0–296)	125 (0–302)
Breath samples taken at end of list (p p m)	47 (20–71)	87 (16–54)	254 (109–396)

POSTER PRESENTATIONS

Is an electronic data collecting device a valid method for assessing postoperative pain in an ambulatory surgery setting?

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The Visual Analogue Scale (VAS) is widely used in the assessment of postoperative pain.[1 2] This can generate large quantities of paper to be stored, plus transcription to databases for analysis may lead to error. We have developed an electronic device to obtain and store VAS pain score data (EPIC glide) and then download these data directly into a computer database.

Fifty-four ambulatory surgery patients, ages 18–63, were enrolled before their surgery. The investigators then made hourly postoperative visits until the patients were discharged. At each visit the patients were asked to perform four VAS pain scores, alternating between the EPIC device and pen and paper. The VAS testing order was alternated at each time point and all prior responses were concealed An additional question on ease of use was asked at completion of the trial.

The data were analysed using a Bland Altman plot (Figure 5).[3] Mean and standard deviations were calculated, using SPSS v9.0, for the differences in VAS pain scores of the two measurement methods and for repeatability within each method.

The electronic patient data collection device has been shown to be easy to use (98%) and comparable to traditional pen and paper VAS pain scoring in an ambulatory surgery setting. In addition there is good agreement between consecutive measurements by either method.

Keywords: pain, evaluation; equipment

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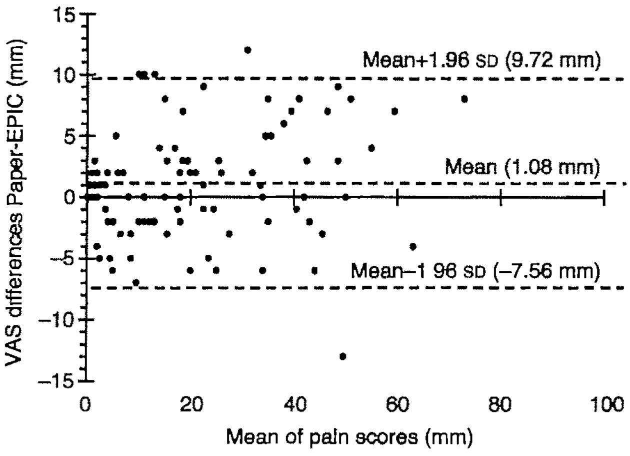

Fig 5 Bland Altman plot for paper and EPIC VAS pain scores

Efficacy of transcutaneous spinal electroanalgesia in patients with chronic neck pain

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Modified TENS machines, which are capable of delivering extremely brief (4 µs) electrical pulses have recently been developed.[1] These are thought to penetrate deep enough to exert modulating effects within the spinal cord. This technique is called transcutaneous spinal electroanalgesia (TSE) Unlike conventional TENS, TSE electrodes do not induce tingling. Therefore, the active treatment mode can be blinded using placebo.

Twenty patients with chronic nociceptive neck pain associated with degenerative changes on x-ray were recruited in this randomised double-blind crossover trial. Exclusion criteria included neuropathic pain. Full instruction in the use of the machine was given. Each patient received active or sham (TSE box with dummy electrodes) treatment for 1 week, a 'washout-period' of no treatment for 1 week and then another 1-week treatment. Patients self-administered therapy of 30 min duration twice daily (as recommended by the manufacturers). Randomization was by the sealed envelope technique and the investigators were blinded throughout the study period. Before the study, 10-cm visual analogue score (VAS) for pain and sleep interference and the SF-36 quality of life questionnaire were completed. Also, VAS for pain and sleep interference were recorded daily by the patient in a diary. Further SF-36 questionnaires were completed at the beginning and end of each treatment session. Power analysis, using data from Ghomane and colleagues,[2] revealed that 20 patients would be needed to detect a difference of 1.3 cm in VAS pain score. Statistical analysis was carried out using a paired Student's *t*-test and Wilcoxon signed ranks test as appropriate. Total area under the daily pain and sleep interference scores were calculated using GraphPad Prism Version 2.0.

There was no significant difference in the change in VAS scores (i.e. difference between beginning and end of treatment), AUC pain score and AUC sleep interference (Table 18). In addition there were no differences in any of the quality of life components of the SF-36 (physical functioning, role physical, role mental, social functioning, mental health, energy, pain, health perception).

We have failed to demonstrate a clinically significant benefit of TSE in this population of patients attending a chronic pain clinic.

Keywords: pain, chronic; analgesic techniques, transcutaneous spinal electroanalgesia

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Table 18 Change in VAS pain and AUC VAS pain and sleep interference scores

	Sham Mean (SD)	**Active Mean (SD)**	***P* (CI of difference)**
Change in VAS pain (cm)	–0.06 (1 7)	–1.2 (2 27)	0.12 (–0.3 to+2 5)
AUC VAS pain scores (cm day)	27 4 (12.8)	26.8 (11 2)	0.64 (–2 2 to+3 5)
AUC VAS sleep interference (cm day)	25.0 (13 6)	22 7 (12.4)	0 42 (–3 2 to+7.7)

Guide to Contributors

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Acknowledgements

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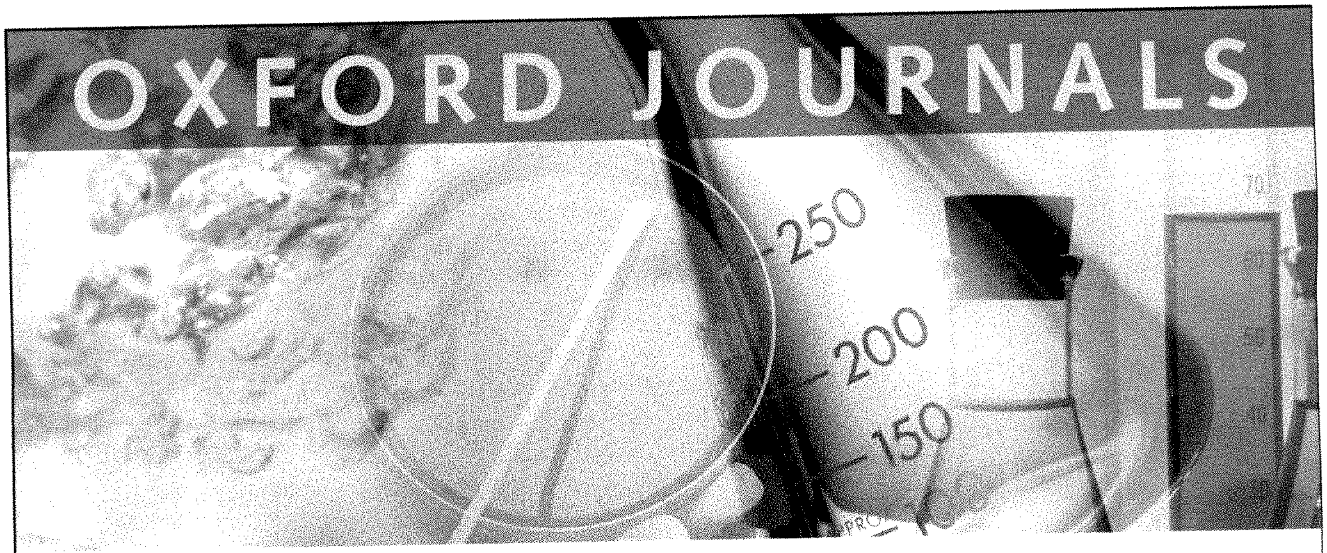

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Pacific Health is committed to the provision of excellent secondary care to it's population. Currently it seeks to deliver these services through two integrated hospitals. This regional focus will continue and intensify. Whakatane Hospital is a 140 bed facility providing general surgery, obstetrics and gynaecology, orthopaedics and ENT, for it's catchment population of 50,000. There is capacity within the existing facility to provide more elective surgery for the wider region. It is for this reason that more anaesthetic input is required. Tauranga, one hour to the west, has a 350 bed hospital with a full range of surgical services (with the exception of neuro and cardiothoracic).

It is essential that applicants are registrable with the New Zealand Medical Council as Specialists with the FANZCA or its equivalent. The present establishment at Whakatane is four anaesthetists, two positions are filled by permanent staff and the remaining two positions have in recent times been supplemented by anaesthetic locums. However there is a renewed determination to obtain permanent staff at specialist grade level. The link with Tauranga Hospital will provide collegial support for a more diverse work experience including private practice.

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Contact Karen Smith, General Manager, Whakatane Hospital,
Ph +64 7 306 0999, Fax +64 7 307 0451 email: karen.smith@bopdhb.govt.nz

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BJA
International Journal of Anaesthesia
Volume 88 Number 3 March 2002

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329 I. Development and use of scoring systems for assessment of clinical competence
R. J. Glavin and N. J. Maran

330 II. Role of the kidney in perioperative inflammatory responses
R. C. Baker, M. A. Armstrong, S. J. Allen and W. T. McBride

334 III. Anaesthesia and the Internet
M. Nyabadza and S. Das

CLINICAL INVESTIGATIONS

338 Use of a high-fidelity simulator to develop testing of the technical performance of novice anaesthetists
F. C. Forrest, M. A. Taylor, K. Postlethwaite and R. Aspinall

345 A prospective study of the quality of pre-hospital emergency ventilation in patients with severe head injury
M. Helm, J. Hauke and L. Lampl

350 Continuous and intermittent cardiac output measurement: pulmonary artery catheter *versus* aortic transpulmonary technique
G. Della Rocca, M. G. Costa, L. Pompei, C. Coccia and P. Pietropaoli

357 Cerebrovascular carbon dioxide reactivity in children anaesthetized with sevoflurane
D. A. Rowney, R. Fairgrieve and B. Bissonnette

362 Recovery of memory after general anaesthesia: clinical findings and somatosensory evoked responses
I. Rundshagen, K. Schnabel and J. Schulte am Esch

369 Noise in the postanaesthesia care unit
B. Allaouchiche, F. Duflo, R. Debon, A. Bergeret and D. Chassard

374 Remifentanil by patient-controlled analgesia compared with intramuscular meperidine for pain relief in labour
J. A. Thurlow, C. H. Laxton, A. Dick, P. Waterhouse, L. Sherman and N. W. Goodman

379 Addition of meperidine to bupivacaine for spinal anaesthesia for Caesarean section
S.-C. Yu, W. D. Ngan Kee and A. S. K. Kwan

384 Abdominal pressure during laparoscopy: effects of fentanyl
G. B. Drummond and M. K. Duncan

389 Phonomyography of the corrugator supercilii muscle: signal characteristics, best recording site and comparison with acceleromyography
T. M. Hemmerling, F. Donati, P. Beaulieu and D. Babin

394 Effect of different pulses of nitric oxide on venous admixture in the anaesthetized horse
E. Heinonen, G. Nyman, P. Meriläinen and M. Högman

LABORATORY INVESTIGATIONS

399 Role of nitric oxide and cyclooxygenase pathways in the coronary vascular effects of halothane, isoflurane and desflurane in red blood cell-perfused isolated rabbit hearts
M. Beaussier, S. Mouren, R. Souktani, M. Arthaud, L. Massias, E. Vicaut, A. Lienhart and P. Coriat

408 Inhaled olprinone improves contractility of fatigued canine diaphragm
A. Uemura, Y. Fujii and H. Toyooka

412 Effects of propofol on lactate accumulation and oedema formation in focal cerebral ischaemia in hyperglycaemic rats
H. Ishii, T. Arai, H. Segawa, S. Morikawa, T. Inubushi and K. Fukuda

REVIEW

418 The role of non-technical skills in anaesthesia: a review of current literature
G. C. L. Fletcher, P. McGeorge, R. H. Flin, R. J. Glavin and N. J. Maran

SHORT COMMUNICATION

430 Effects of remifentanil and alfentanil on the cardiovascular responses to induction of anaesthesia and tracheal intubation in the elderly
A. S. Habib, J. L. Parker, A. M. Maguire, D. J. Rowbotham and J. P. Thompson

CASE REPORTS

434 Management of life-threatening autonomic hyper-reflexia using magnesium sulphate in a patient with a high spinal cord injury in the intensive care unit
N. A. Jones and S. D. Jones

438 Lumbar ependymoma presenting with paraplegia following attempted spinal anaesthesia
M. Jaeger, E. Rickels, A. Schmidt, M. Samii and U. Blömer

440 Intraoperative pulmonary oedema in a child following systemic absorption of phenylephrine eyedrops
F. J. Baldwin and A. P. Morley

443 Value of bispectral index monitoring during cardiopulmonary resuscitation
B. Szekely, T. Saint-Marc, A.-C. Degrémont, M.-H. Castelain and M. Fischler

HISTORY

445 The British Journal of Anaesthesia. An informal history of the first 25 years
J. Norman

451 CORRESPONDENCE

460 BOOK REVIEWS

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References
1. Eli Lilly and Company. Data on file. Source of data: The Intensive Care National Audit & Research Centre. 2. Natanson C et al. *Crit Care Med* 1998;26:1927–31.
† throughout England, Wales and Northern Ireland; ‡ defined as sepsis associated with acute organ dysfunction; § these figures do not include cases of severe sepsis that occur either on wards or after the first 24 hours in the ICU.

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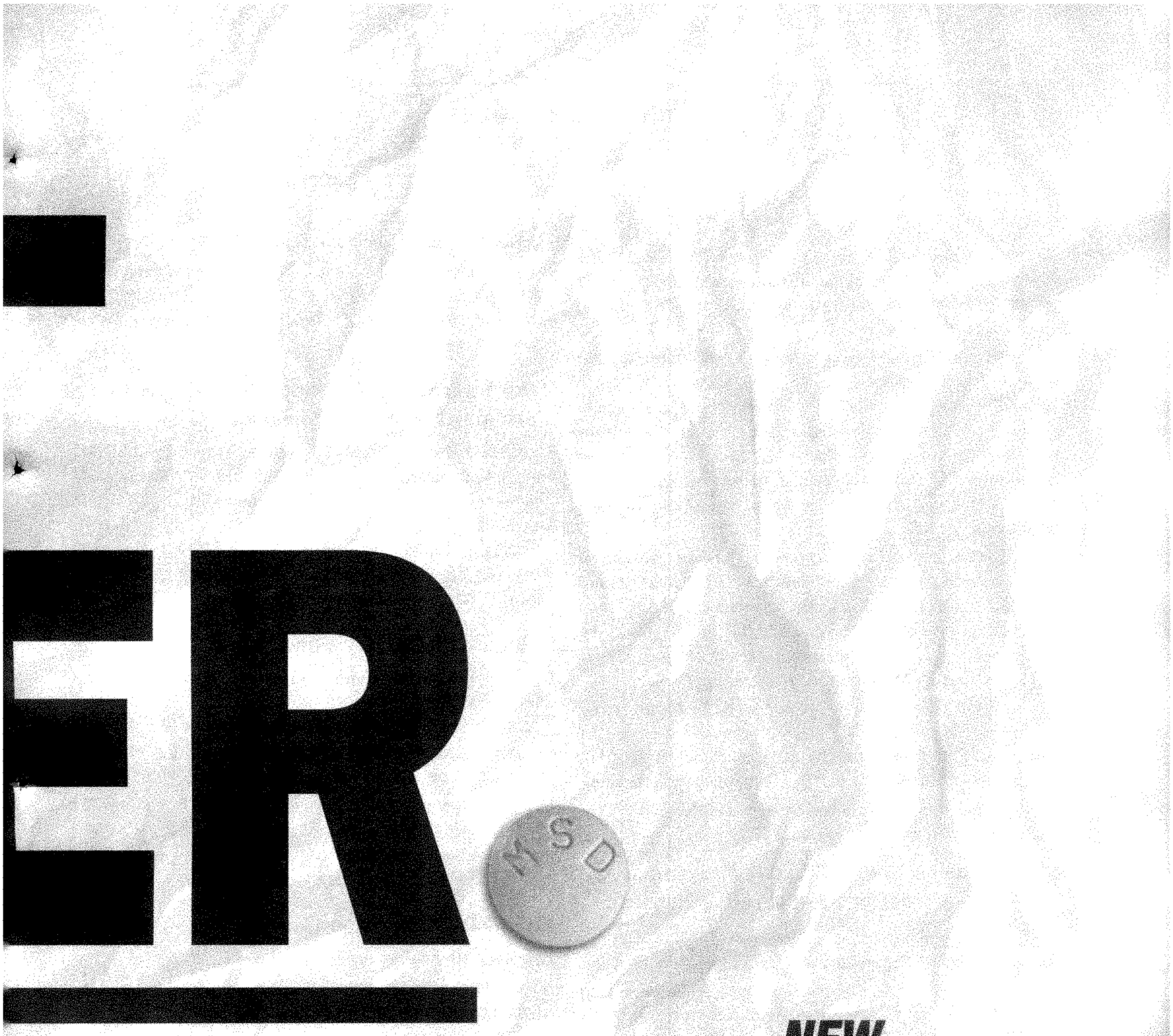
PRECAUTIONS

Consider monitoring renal function in patients with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis. Use caution when initiating treatment in patients with considerable dehydration. Rehydrate patients prior to starting therapy with rofecoxib. Consider the possibility of fluid retention and exercise caution when rofecoxib is used in patients with pre-existing oedema, a history of heart failure, left ventricular dysfunction or hypertension. Maintain appropriate supervision when treating the elderly or patients with renal, hepatic or cardiac dysfunction with rofecoxib. Rofecoxib may mask fever. Use of rofecoxib is not recommended in women attempting to conceive. In clinical studies, some osteoarthritis (OA) patients treated with rofecoxib developed perforations, ulcers or bleeds (PUBs). Patients with a prior history of a PUB and patients greater than 65 years of age appeared to be at a higher risk for a PUB. At chronic daily doses higher than 25 mg, the risks of gastro-intestinal symptoms, oedema or hypertension are increased. Elevations of ALT and/or AST (≥3 times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with rofecoxib. Any patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated. *Interactions (pharmacodynamic): Warfarin:* closely monitor the prothrombin time INR when therapy with
rofecoxib is initiated or changed in patients receiving warfarin or similar agents, particula
first few days. *ACE-inhibitors:* administration of 25 mg daily of rofecoxib with benazepr
to 40 mg daily for four weeks to patients with hypertension was associated with a small at
of the antihypertensive effect compared to the ACE inhibitor alone. This should be cons
patients taking rofecoxib concomitantly with ACE inhibitors. *Beta-blockers and diuretics:* co
use of NSAIDS may reduce the antihypertensive efficacy of beta-blockers and diuretics an
effects of diuretics. *Aspirin:* at steady state, rofecoxib 50 mg once daily had no effect or
platelet activity of low-dose (81 mg once daily) aspirin. Avoid concomitant administration of
with higher doses of aspirin or other NSAIDS. *Cyclosporin/tacrolimus:* monitor renal funct
rofecoxib and either cyclosporin or tacrolimus is used in combination. *Interactions (pharm*
Lithium: NSAIDS may increase plasma lithium concentrations. *Methotrexate:* consider
monitoring for methotrexate-related toxicity when rofecoxib and methotrexate are adr
concomitantly. *CYP1A2 substrates:* exercise care with concomitant administration of rofe
drugs primarily metabolised by CYP1A2 (e.g. theophylline, amitriptyline, tacrine and
Midazolam: a modest 30% reduction of the AUC of midazolam was seen with rofecoxib 2
most likely due to increased first pass metabolism through induction of intestinal CYP3
by rofecoxib. *CYP3A4 substrates:* in spite of a modest induction of intestinal CYP3A4 a
pharmacokinetics of drugs metabolised primarily by CYP3A4 are not expected to be af
clinically significant extent. However exercise care when co-prescribing substrates of CY



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ECTS

ing drug-related undesirable effects were reported at an incidence greater than 1% and n placebo in analgesia clinical studies in patients treated with rofecoxib 50 mg or 25 mg ays: dizziness, diarrhoea, diaphoresis, dyspepsia. The following drug-related undesirable e reported at an incidence greater than placebo in osteoarthritis clinical studies in patients h rofecoxib 12.5 mg or 25 mg for up to six months, or in post-marketing experience. *(≥1/100, <1/10); Uncommon (≥1/1000, <1/100); Rare (≥1/10,000, <1/1000); Very 0,000) and isolated cases]*

whole/site unspecified: *Common:* oedema/fluid retention, abdominal pain, dizziness. : asthenia/fatigue, abdominal distension, chest pain. *Very rare:* hypersensitivity reactions, ngioedema, urticaria and anaphylactic/anaphylactoid reactions. ***Blood and the lymphatic system disorders:*** *Common:* haematocrit decreased. *Uncommon:* haemoglobin decreased, erythrocytes decreased, leukocytes decreased. *Very rare:* thrombocytopenia. ***Cardiovascular system:*** *Common:* hypertension. *Very rare:* congestive heart failure. ***Digestive system:*** *Common:* heartburn, epigastric discomfort, diarrhoea, nausea, dyspepsia. *Uncommon:* constipation, oral ulcer, vomiting, digestive gas symptoms, acid reflux. *Rare:* peptic ulcers, gastro-intestinal perforation and bleeding (mainly in elderly patients), gastritis. ***Hepatobiliary disorders:*** *Common:* alanine aminotransferase increased, aspartate aminotransferase increased. *Uncommon:* alkaline phosphatase increased. *Isolated cases:* hepatotoxicity including hepatitis and jaundice. ***Eyes, ears, nose and throat:*** *Uncommon:* tinnitus. *Very rare:* blurred vision. ***Metabolism and nutrition:*** *Uncommon:* weight gain. ***Musculoskeletal:*** *Uncommon:* muscular cramp. ***Nervous system:*** *Common:* headache. *Uncommon:* insomnia, somnolence, vertigo. *Very rare:* paraesthesia. *Isolated cases:* aseptic meningitis. ***Psychiatric disorder:*** *Uncommon:* depression, mental acuity decreased. *Very rare:* confusion, hallucinations. ***Respiratory system:*** *Uncommon:* dyspnoea. *Very rare:* bronchospasm. ***Urogenital:*** *Uncommon:* BUN increased, serum creatinine increased, proteinuria. *Very rare:* renal insufficiency, including renal failure, usually reversible upon discontinuation of therapy. ***Skin and skin appendages:*** *Common:* pruritus. *Uncommon:* rash, atopic dermatitis. *Very rare:* alopecia. *Isolated cases:* cutaneo-mucosal adverse effects and severe skin reactions including Stevens-Johnson Syndrome. In clinical studies, the undesirable effects profile was similar in patients treated with rofecoxib for one year or longer. The following serious adverse effects have been reported in association with the use of NSAIDs and cannot be ruled out for rofecoxib: nephrotoxicity including interstitial nephritis and nephrotic syndrome; hepatotoxicity including hepatic failure.

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Editorial Notices

BJA/RCA RESEARCH FELLOWSHIPS and GRANTS

The *British Journal of Anaesthesia, in conjunction with the Royal College of Anaesthetists* is making a further round of grants available to support research in anaesthesia, intensive care or pain relief.

Project Grants are available to support specific research in anaesthetic departments. Joint applications with basic science departments will be welcome. These grants may be awarded to fund technical staff, research students or post-doctoral research fellows; salaries, or items of equipment. The maximum value of any award will be £50 000, and the *BJA/RCA* will not contribute towards overheads.

The *BJA/RCA* will also consider funding **Research Fellowships** with this round of awards. Applicants should note that candidates will usually be members of academic departments of anaesthesia; and the grant must be administered by an academic department of anaesthesia and have the support of the head of that department.

For further details and forms, please **write** or **Email** to: Dr J. W. Sear (BJA Grants Officer), Nuffield Department of Anaesthetics, University of Oxford, John Radclife Hospital, Headington, Oxford OX3 9DU *or* john.sear@nda.ox.ac.uk

Closing date for applications is **April 30th, 2002**. Late applications will **not** be considered.

Key Advances in the Effective Prevention and Management of Postoperative Nausea and Vomiting

Royal College of Physicians of London, March 18, 2002

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For further information please contact: Mrs Pat Fleming; Tel: +44 (0)20 8525 8665; Email: pat@keyadvances3.demon.co.uk

International Anaesthesia Research Society Annual Clinical and Scientific Congresses

March 16–20, 2002

IARS 76th Clinical and Scientific Congress, San Diego Marriott Hotel & Marina, San Diego, California, USA.

March 22–26, 2003

IARS 77th Clinical and Scientific Congress, New Orleans Marriott, New Orleans, Louisiana, USA.

March 27–31, 2004

IARS 78th Clinical and Scientific Congress, Tampa Marriott Waterside Hotel, Tampa, Florida, USA.

March 11–15, 2005

IARS 79th Clinical and Scientific Congress, Hilton Hawaiian Village, Honolulu, Hawaii, USA.

Contact information: IARS, 2 Summit Park Drive, Suite 140, Cleveland, OH 44131, USA. Tel: +1 216 642 1124; Fax: +1 216 642 1127; Email: iarshq@iars.org; Web: www.iars.org

22nd International Symposium on Intensive Care and Emergency Medicine

Congress Center, Brussels, Belgium, March 19–22, 2002

For further details, please contact: Mrs Veronique de Vlaeminck, Department of Intensive Care, Erasme University Hospital, Route de Lennik 808, B-1070 Brussels, Belgium. Tel: +32 2 555 32 15/36 31; Fax: +32 2 555 45 55; Email: Veronique.De.Vlaeminck@ulb.ac.be Website: http://www/intensive.org

Primary FRCA Revision Course

Clinical Education Centre, Glenfield Hospital, March 20–22, 2002

An intensive revision course for the Primary FRCA based on small group tutorials and including written and oral examination practice.

Fees: £250 non-residential (including lunch and refreshments). Places are strictly limited.
For a booking form, please contact: Christine Gethins. Tel: +44 (0)116 258 5291; E-mail: anae@le.ac.uk

Final FRCA Revision Course

Leicester Royal Infirmary, April 8–11, 2002

An intensive revision course for the Final FRCA based on small group tutorials and including written and oral examination practice.

Fees: £290 including lunch and refreshments; £335 with 3 nights accommodation; £350 with 4 nights accommodation. Places are strictly limited.
For a booking form, please contact: Christine Gethins. Tel: +44 (0)116 258 5291; Email: anae@le.ac.uk.

Advances in Minimally Invasive Hand/Upper Extremity Surgery

Genval (Brussels), Belgium, April 19–20, 2002

The symposium will promote exchange between scientists and clinicians, and will include presentations by invited faculty. Participants may submit original papers for a limited number of oral presentations, and there will be considerable time reserved for discussion. Deadline for submission of abstracts: December 31, 2001.

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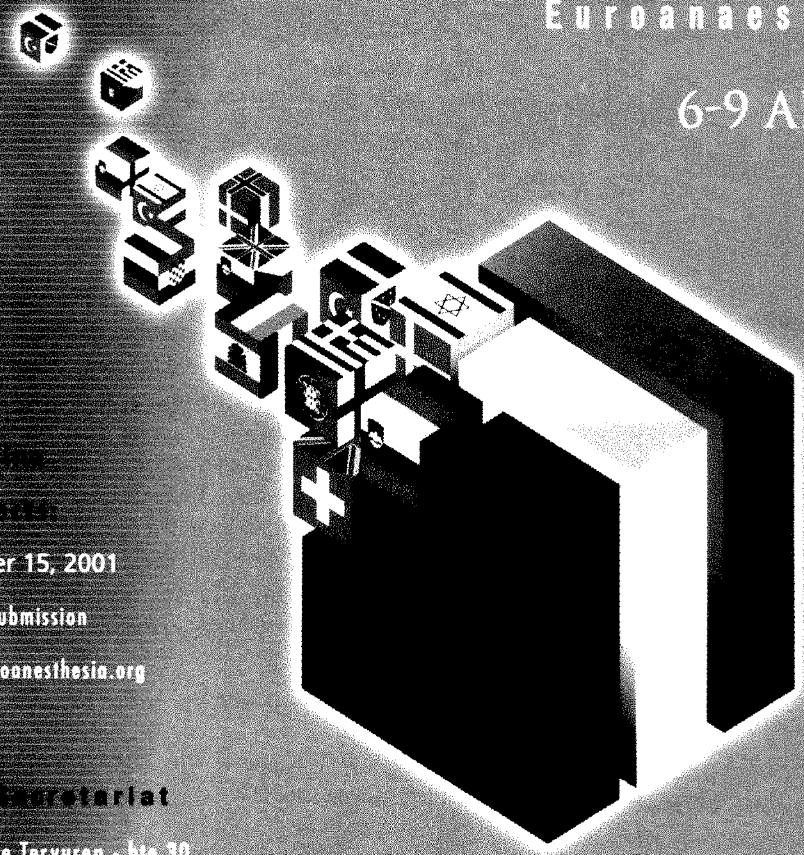

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Artificial Oxygen-carriers: a Clinical Future?

The Royal College of Physicians of Edinburgh, Edinburgh, May 9, 2002

Speakers to include Dr John Hess, Professor Donat Spalm, Dr J. Maguire and Dr Dafydd Thomas. With contributions from the major companies attending a prior workshop.

For further details, please visit the website: http://www.rcpe.ac.uk/AOCs or Tel: +44 (0)131 225 7324; Fax: +44 (0)131 220 4393

Putting New Flesh on Old Bones: a major conference on Issues in the Perioperative Care of Geriatric Trauma

The Netherwood Hotel, Grange-Over-Sands, UK, May 10, 2002

Speakers include: Nigel Sharrock (New York); Martyn Parker (Peterborough)

Deadline for free paper abstracts: February 1, 2002.

Please contact Dr Andrew Severn for details: Tel: +44 (0)1524 583517; Fax: +44 (0)1524 583519.

Australian and New Zealand College of Anaesthetists Annual Meeting

Brisbane Convention and Exhibition Centre, Brisbane, Australia, May 11–15, 2002

For further information please contact:

ANZCA 2002 Secretariat, PO Box 1280, Milton QLD 4064, Australia.

Tel: +61 (0) 7 3858 5537; Fax: +61 (0) 7 3858 5510;
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Royal Australasian College of Surgeons and The Royal College of Surgeons of Edinburgh, Annual Scientific Congress

Adelaide, Australia, May 11–15, 2002

A joint meeting of the colleges to celebrate the 75th anniversary of the Australasian College. A team of speakers will address: Clinical Governance, Quality in Surgical Education, Remote and Rural Surgery, Medical Legal Problems, Colorectal Surgery, Paediatric Surgery, and Trauma.

Closing date for abstracts: January 25, 2002. Abstracts should be submitted electronically: http://www.surgeons.org

Registration for Fellows of the Royal College of Surgeons of Edinburgh will be through this College. Please contact: Mrs Maureen Lowrie in the Education Section of the College. Tel: +44 (0)131 668 9209; Fax: +44 (0)131 668 9241. Email: m.lowrie@rcsed.ac.uk

First World Congress on Regional Anaesthesia and Pain Therapy

Barcelona, Spain, June 5–8, 2002

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; Email: dionne@options.com.cy

Ralph M. Waters, MD, and Professionalism in Anesthesiology: A Celebration of 75 years

The Concourse Hotel & Governor's Club, Madison, Wisconsin, USA, June 6–8, 2002

A combined meeting of Anesthesia History Association (US) and History of Anaesthesia Society (Great Britain) with additional sponsors: University of Wisconsin Medical School, Department of Anesthesiology and Office of Continuing Medical Education, Wisconsin Society of Anesthesiologists, and Wood Library-Museum of Anesthesiology. This conference will celebrate the arrival of Ralph M. Waters, MD, in Madison, Wisconsin, in 1927, and explore his legacy in anaesthesia practice and professionalism. Abstracts are invited on any aspect of his career and legacy and also on any aspect of anaesthesia history related to the three broad areas of professionalism to which Dr Waters contributed: (1) education; (2) research; and (3) creation of specialty societies designed to promote improvements in the clinical and ethical standards of practice in anaesthesiology. Abstract deadline: March 1, 2002.

Conference information: Mark E. Schroeder, MD, Associate Professor, Department of Anesthesiology, University of Wisconsin Medical School, 600 Highland Avenue, Room B6/319, Madison, WI 53792-3272, USA. Tel: +1 608 203 8105; Fax: +1 608 262 6247; Email: aha2002@anesthesia.wisc.edu; website: http://www.anes.uab.edu/anehist/watersconf.htm

XVIth Edinburgh Anaesthesia Festival

Edinburgh, UK, August 21–23, 2002

A three-day programme consisting of lectures and discussion on current topics in anaesthesia.

For further details, please contact: University Department of Anaesthesia, Critical Care and Pain Medicine, Royal Infirmary, Lauriston Place, Edinburgh EH3 9YW, UK.

Tel: +44 (0)131 536 3652; Fax: +44 (0)131 536 3672. Email: anaes@ed.ac.uk

Anaesthesia outside the square: CECANZ Conference 2002

Christchurch, New Zealand, September 18–20, 2002

For information, please contact: Conference Secretariat Joy Mehlhopt, Conference Innovators, P.O. Box 1370, Christchurch, New Zealand.

Tel: +61 3 379 0390; Fax: +61 3 379 0460; E-mail: joy@conference.co.nz. Website: www.cecanz2002.org.nz

Société Française d'Anesthésie et de Réanimation

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September 18–21, 2003
September 20–October 3, 2004
September 29–October 2, 2005

For further information, please contact: SFAR, 74, rue Raynouard, F-75016 Paris, France. Tel: +33 1 45 25 82 25; Fax: +33 1 40 50 35 22; E-mail SFAR@invivo.edu

Dingle 2002—4th Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 2–6, 2002

For further information contact: Dr Monty Mythen, Director, Centre for Anaesthesia, UCL, Room 103, 1st Floor Crosspiece, Middlesex Hospital, London, W1T 3AA, London, UK. Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com

Australian Society of Anaesthetists National Scientific Congress

Adelaide, Australia, October 26–30, 2002

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For further details, please contact: Festival City Conventions, P.O. Box 949, Kent Town, S.A. 5071, Australia. Tel: +61 (0)8 8363 1307; Fax: +61 (0)8 8363 1604: E-mail: asa2002@fccconventions.com.au

8th International Congress of Cardiothoracic and Vascular Anesthesia

19th International Congress of the Israel Society of Anesthesiologists

Jerusalem, Israel, November 10–13, 2002

For further information regarding the Congress, please contact:

8th International Congress of Cardiothoracic and Vascular Anesthesia, PO Box 50006, Tel Aviv 61500, Israel

Tel: +972 3 5140000; Fax: +972 3 5140077; E-mail: anesth2002@kenes.com

Web address: http://www.isranest.org.il/congress 2002

German Congress of Anaesthesiology 2002 (DAK 2002)

Messezentrum Nürnberg, June 26–29, 2002

German Congress of Anaesthesiology 2003

(DAK 2003)

Messezentrum Nürnberg, June 18–21, 2003

For further information, please contact:

Medizinisch Congressorganization Nürnberg AG.
Tel: +49 911 393160; Fax: +49 911 331204

27th Congress of The Scandinavian Society of Anaesthesiology and Intensive Care Medicine

Helsinki, Finland, August 16–20, 2003

A biannually arranged Scandinavian congress in one of the five Scandinavian countries; language: English.

For further information please contact: Prof. Per H.Rosenberg, Helsinki University Hospital, Helsinki FIN00029 HUS, Finland.

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Dingle 2003—5th Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 1–5, 2003

For further information contact:

Dr Monty Mythen, Director, Centre for Anaesthesia, UCL, Room 103, 1st Floor Crosspiece, Middlesex Hospital, London, W1T 3AA, London, UK. Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com

13th World Congress of Anaesthesiologists

Palais des Congrès de Paris, Paris, France, April 18–23, 2004

For further details, please contact the Congress Office at: COLLOQUIUM, 12 rue de la Croix Faubin, F-75557 Paris cedex 11, France. Tel: +33 (0) 1 44 64 15 15 Fax· +33 (0) 1 44 64 15 16/17. Email: wca2004@colloquium.fr Website: www.wca2004.com

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BRITISH JOURNAL OF ANAESTHESIA

Volume 88, Number 3, March 2002

Editorial I

Development and use of scoring systems for assessment of clinical competence

The assessment of clinical competence is one of the greatest challenges facing medicine today. A useful construct for the assessment of competence is provided in the Miller pyramid (Fig. 1).[1]

The first two stages, 'knows' and 'knows how', can be assessed using the traditional assessment tools of written and oral tests. However, 'knowing' and 'knowing how' clearly do not necessarily extrapolate to the application of knowledge in the workplace. To demonstrate clinical competence, assessment at levels 3 and 4 becomes more important, but also more challenging. Level 3, 'shows how', is currently assessed by practical examinations, observed long or short cases, or OSCE style examinations. However, the only way to assess level 4, 'does', is to observe the practitioner at work in the real world.

Assessment tools developed for this purpose should allow us to compare performance with some pre-existing standard. They should also allow us to identify deficiencies in the performance of the person being assessed, so that subsequent training can be targeted to the areas of greatest need. This requires that we break performance down into more manageable and identifiable components, and this is normally achieved using scoring systems.

The first challenge is therefore to identify the important constituent parts of good medical practice that should make up the elements of the scoring system. We can examine our current practice and seek out those components necessary for good performance. In this issue, Forrest and colleagues[2] describe the use of a modified Delphi technique to develop a scoring system for assessment. First used in the 1950s,[3] this technique seeks to gain a consensus from a group of experts in response to an open-ended question. It has become popular in a wide range of fields, including economics and social policy as well as health-care. The Delphi technique involves sending an initial questionnaire to a group of identified experts. This will generate a variety of responses and ideas, and these are collated and form the basis of the second questionnaire, which is sent to the same group of experts. Subsequent responses are handled statistically to produce relative frequencies, and continued review by the expert group gives them the opportunity to change their mind or include any other items. This process is repeated until consensus is reached, which may require as many as 10 rounds, although this is often reduced when the modified technique is used. Keeney and colleagues have recently published a critical review of the use of the technique in nursing research.[4] While the Delphi technique works well to identify the key technical skills involved in a process such as rapid sequence induction, one of the drawbacks of asking experts to identify all attributes of clinical competence is that they may not be conscious of the full range of these components. Many aspects of expert performance have become intuitive[5] and may not be readily accessible by individuals. Much of anaesthetic practice involves a cognitive component, which is also not readily accessible using techniques such as a Delphi process. This poses the question of how complete the Delphi technique can be in providing the material from which a scoring system to assess clinical competence will be compiled. Any scoring system that attempts to address the assessment of clinical competence clearly has to address both technical and non-technical skills.

The technique of cognitive task analysis is designed to access the key non-technical skills which underpin performance, such as decision making, problem solving, attention allocation, planning and workload management. It uses a combination of methods, such as observation and interview, to 'unpack and make explicit the expert knowledge that is often implicit and difficult for analysis to

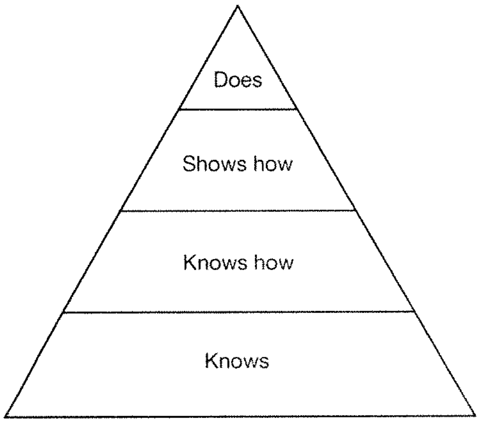

Fig 1 The Miller pyramid.

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observe or for experts to verbalise'.[6] These methods are clearly more time-consuming and specialist, but have been used extensively in other high-reliability industries and have been used more recently in anaesthesia to identify key components.[7]

The identified components must be assembled into a scoring system that satisfies the characteristics of a good assessment tool, namely, validity, reliability and feasibility.[8] The scoring system must then undergo pilot testing to demonstrate that it has these characteristics. Forrest and colleagues have addressed all of these issues.[2] The *content validity* (the extent to which the assessment representatively samples what it is supposed to be measuring) of their scoring system is high, given the methods used to develop their tool. *Construct validity* (the extent to which a new measure is related to specific variables in accordance with a hypothetical construct) is also high, given that they were able to demonstrate improved scores with increasing clinical experience. They also were able to demonstrate good *inter-rater reliability*, using multiple assessors to score the same performance. They have demonstrated the potential role of the simulator in the testing of an assessment tool, and they established the feasibility of using their scoring system to rate performance from videos of performance in the simulator. However, such a detailed scoring system may be more challenging to use during real-time observation in clinical practice.

The final challenge of developing a new assessment tool is to ensure that the subjects have confidence not only in the tool itself but also in those carrying out the assessment. This becomes increasingly important as we venture into assessment outside the traditional framework of knowledge and skills, and as the stakes involved increase. This requires that those carrying out the assessment have had sufficient training in its application to ensure not only that the assessment is fair but also that it is seen to be fair. The higher the stakes, the more important it is that all of these challenges have been met properly. Judgement of clinical incompetence and its impact on the career of the subject must be defensible from legal challenge. The assessment systems of the future will not only be used to ensure the competence of our trainees, but they will also stand to become the tools of revalidation. Every one of us will then be subjected to them. It is time to take assessment seriously.

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Editorial II

Role of the kidney in perioperative inflammatory responses

Perioperative inflammatory responses are relatively well characterized. Increases in the plasma proinflammatory cytokines interleukin (IL)-1β, tumour necrosis factor α (TNF-α) and IL-8 are later accompanied by increases in the anti-inflammatory cytokines IL-10, IL-1 receptor antagonist (IL-1ra) and TNF-α soluble receptors (TNF-sr)—the so-called phased anti-inflammatory response (PAIR).[1–3] Proinflammatory cytokines act locally and in health are rarely detectable in plasma. In contrast, anti-inflammatory cytokines such as IL-1ra and TNF-sr are present in plasma in measurable concentrations. The molecular weights of IL-1β, IL-8 and monomeric TNF-α are less than 20 kDa, rendering rapid glomerular filtration possible. As the biologically active form of TNF-α is a trimer (51 kDa) in equilibrium with the dimeric and monomeric forms, rapid filtration of the

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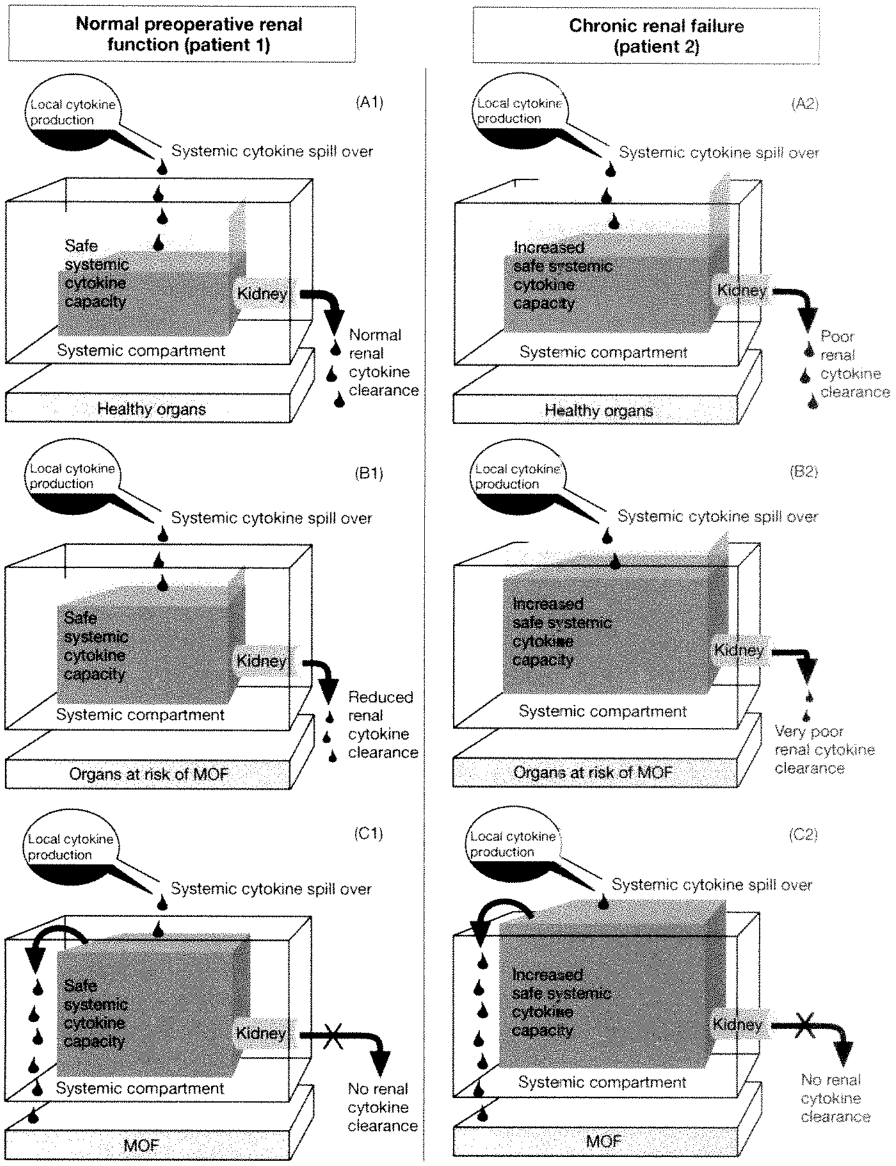
Normal preoperative renal function (patient 1)
Chronic renal failure (patient 2)
(A1)
Local cytokine production
Systemic cytokine spill over
Safe systemic cytokine capacity
Kidney
Normal renal cytokine clearance
Systemic compartment
Healthy organs
(A2)
Local cytokine production
Systemic cytokine spill over
Increased safe systemic cytokine capacity
Kidney
Poor renal cytokine clearance
Systemic compartment
Healthy organs
(B1)
Local cytokine production
Systemic cytokine spill over
Safe systemic cytokine capacity
Kidney
Reduced renal cytokine clearance
Systemic compartment
Organs at risk of MOF
(B2)
Local cytokine production
Systemic cytokine spill over
Increased safe systemic cytokine capacity
Kidney
Very poor renal cytokine clearance
Systemic compartment
Organs at risk of MOF
(C1)
Local cytokine production
Systemic cytokine spill over
Safe systemic cytokine capacity
Kidney
No renal cytokine clearance
Systemic compartment
MOF
(C2)
Local cytokine production
Systemic cytokine spill over
Increased safe systemic cytokine capacity
Kidney
No renal cytokine clearance
Systemic compartment
MOF

Fig. 1 Conceptualized diagram representing two patients undergoing a simultaneous inflammatory insult of identical intensity, such as major cardiovascular surgery. Patient 1 has normal preoperative renal function and patient 2 has chronic renal impairment. (Time A) During the initial phase of the insult in both patients, local cytokine production spills into the systemic compartment. In patients 1 and 2 this is countered by two strategies: *strategy 1* is renal excretion of proinflammatory cytokines; *strategy 2* consists of anti-inflammatory mechanisms that are constitutively active in plasma. The notional quantity of proinflammatory cytokines safely controlled by these plasma anti-inflammatory mechanisms is represented by the box labelled 'Safe systemic cytokine capacity'. To compensate for a defect in strategy 1, patient 2 has preoperatively developed strategy 2, as indicated by an increased safe systemic cytokine capacity. At this time point, organs in both patients are still 'safe'. (Time B) In both patients, the kidneys undergo significant injury. This may be due either to the inflammatory response itself or to an additional hypotensive episode. Strategy 1 has now been knocked out and if the spillover of inflammatory mediators continues at a constant rate, strategy 2 is in danger of being overwhelmed, resulting in multiple organ failure (MOF). However, because patient 2 has compensated for a defective strategy 1 preoperatively by the use of the more effective strategy 2 (box labelled 'Increased safe systemic cytokine capacity'), the impact of acute renal failure on inflammatory-mediated organ failure may be delayed. (Time C) The safe systemic cytokine capacity has been exceeded in both patients and proinflammatory mediators can have deleterious effects on other organs. Patients with normal renal function preoperatively who develop acute renal failure in the presence of an ongoing inflammatory response are at particular risk of multiple organ failure.

monomeric form may be expected to reduce the concentration of the biologically active trimer. This may be one reason why the proinflammatory cytokines are rarely detected in health and why, during an inflammatory response, their elevation in plasma is not sustained.[3] In contrast, the anti-inflammatory cytokines are larger than 20 kDa and thus less readily filtered by the kidneys. Not surprisingly, IL-1ra and TNF-srs are present constitutively in plasma at measurable concentrations and provide an immediate control mechanism should elevated TNF-α or IL-1β spill over into the plasma from a local tissue site of inflammation. If the kidney is filtering these proinflammatory cytokines, how does it safely do so, given their known tubulotoxic properties? Does the kidney sacrifice itself for the greater good of the body? Recently, we demonstrated a rapid perioperative increase in urinary anti-inflammatory cytokines (IL-1ra and TNF-srs), suggesting a possible intra-renal protective mechanism during proinflammatory cytokine disposal.[3] Although involved in managing the inflammatory response, the kidney is especially vulnerable to these same proinflammatory processes, particularly if they jeopardize adequate tubular oxygenation or exaggerate pro-apoptotic or pro-necrotic stimuli.[4 5]

Let us consider two stages in the pathogenesis of acute renal failure and evaluate the important impact of inflammatory processes in each.

Stage 1 (transient hypotension). In hypotension, glomerular perfusion pressure falls. This is further accentuated by afferent arteriolar vasoconstriction.[6] This leads to reduced tubular energy expenditure through reduced work of protein and ion reabsorption. Urine is of reduced volume but of 'good quality'. At this stage, if there is a background inflammatory response, hypotension and the leucocyte adhesion potential may be accentuated, although adequate peritubular blood flow will minimize the deleterious consequences of this. Proinflammatory cytokine disposal is still possible.

Stage 2 (persistent hypotension). If hypotension persists, efferent arteriolar vasoconstriction restores glomerular perfusion pressure and normalizes urinary output. Sodium and protein transport energy requirements are restored in the absence of the restoration of tubular oxygen delivery. The reduced flow secondary to hypotension and efferent arteriolar vasoconstriction predisposes to margination of neutrophils along the capillary endothelial walls. Furthermore, the hypoxia resulting from reduced perfusion leads to tubular capillary endothelial adhesion molecule up-regulation and results in increased neutrophil adhesion potential.[7] This now sets up a vicious circle of hypoxia and further neutrophil sludging.[8]

Adhering granulocytes liberate vasoconstrictive and tubulotoxic mediators. These include nitric oxide (NO), superoxide radicals and platelet activating factor. In the face of this inflammatory onslaught, tubular capillary endothelium reacts as if a local infective response has struck, needing urgent containment. Consequently, constitutive dilatory endothelial NO synthase (eNOS) is down-regulated (leading to vasoconstriction) and vasoconstrictive endothelin-1 is released, leading to further vasoconstriction. A key element in this process is neutrophil adhesion.[8]

It is apparent that any evolving systemic septic or proinflammatory response is going to seriously increase leucocyte adhesion potential within the tubular capillaries. For example, marked up-regulation of granulocyte adhesion molecules occurs during cardiopulmonary bypass,[9] abdominal aortic aneurysm surgery[10] and sepsis.[11] Any superimposed hypotension in this context may exaggerate the already heightened adhesion potential within the renal capillaries. At this point, tubular hypoxia is unavoidable.

During all of the above, the kidney is still trying to contain the inflammatory response by filtering out proinflammatory mediators as well as many other substances, many of which may be tubulotoxic. For example, a host of filtered toxins, such as haemoglobin, myoglobin, radiocontrast medium[12] and antibiotics provide pro-apoptotic and pro-necrotic stimuli. Filtered inflammatory mediators may be tubulotoxic. For TNF-α and IL-1β a direct tubulotoxic mechanism has been suggested on the basis of *in vitro* demonstration of cytotoxic NO concentrations arising from activation of inducible NOS (iNOS) in cultured proximal tubular cells.[13 14] In addition to these pronecrotic effects *in vitro* evidence suggests direct pro-apoptotic mechanisms are involved.[15] Recently, correlations were demonstrated between plasma concentrations of both TNF-α and IL-8 and proximal tubular injury in cardiac surgery [as measured by the urinary *N*-acetyl-β-D-glucosaminidase/creatinine ratio].[3]

What happens to the control mechanism of the inflammatory response when the kidney starts to fail?

Acute renal failure is associated with a high incidence of multiple organ failure (MOF) and death. For example, in cardiac surgery the incidence of acute renal failure requiring dialysis (ARF-D) is 1–5%[16–18] Mortality in such circumstances is high, ranging from 28%[19] to 63.7%.[20] Although this high mortality may be due directly to the deleterious effect on non-renal organs of the precipitating renal insult, there are theoretical possibilities that ARF-D itself has deleterious consequences for other organs by adversely modulating the inflammatory response. If the kidney is so important in controlling inflammatory responses, how can patients in chronic renal failure survive major surgery?

During cardiac surgery, the risk of perioperative mortality in patients with preoperative dialysis-dependent chronic renal failure (CRF-D) ranges from zero[21] to 11.4%.[22] Although preoperative CRF-D may lead to an expectation of greater perioperative morbidity and a longer hospital stay,[17] this relatively limited increase in mortality of CRF-D patients may suggest a mechanism of proinflammatory control despite the absence of functioning kidneys. Patients in chronic renal failure, irrespective of dialysis dependence, cannot rely on immediate filtration of proinflammatory mediators as a primary anti-inflammatory mechanism. Their survival during an acute proinflammatory response may rely partly on secondary control mechanisms which, over time, have developed to compensate for the loss of renal immunomodulatory function.[23] Consequently, chronic renal failure patients have a wide range of anti-inflammatory strategies in place.[24–26] These include increased plasma TNF-sr 1 and 2,[27 28] increased IL-1ra,[29] increased granulocyte inhibitory protein[24 30 31] and uraemia. It is important to distinguish between acute and chronic renal dysfunction as risk factors for the development of MOF (Fig. 1).

Application

No longer can the kidney be regarded as a passive bystander in the evolving inflammatory response: it is rather an organ actively involved in the control of the response, even to the extent of sustaining injury in the process. Consequently, clinical strategies of renal protection should also be considered as indirectly protecting other organs against inflammatory-mediated MOF. For example, volume replacement and avoidance of hypotension may reduce the danger of tubular capillary stasis and thus lessen the already heightened risk of tubular damage arising from leucocyte adhesion when there is a background of an ongoing inflammatory response. Furthermore, such measures, by preserving renal ability to remove proinflammatory cytokines, may help restrict the perioperative plasma changes in pro- and anti-inflammatory cytokines to physiologically tolerable limits. The effectiveness of perioperative inflammatory limitation strategies in minimizing renal injury awaits elucidation. When the kidneys fail, it takes time for the remaining plasma anti-inflammatory strategies to be overwhelmed and the resulting uncontrolled inflammatory responses to effect organ damage. It is conceivable that the patient who presents with normal renal function preoperatively has heightened vulnerability compared with the patient with chronic renal dysfunction. This is because the patient with chronic renal dysfunction has developed a greater plasma anti-inflammatory background to compensate for reduced ability to remove the proinflammatory load. Patients with normal renal function preoperatively who develop acute renal failure in the presence of an ongoing inflammatory response are at particular risk of MOF. Renal protective strategies should be considered as indirectly anti-inflammatory.

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Editorial III

Anaesthesia and the Internet

As with many technological developments that eventually benefit mankind, the original intention of the Internet was for military advantage. Following the launch of Sputnik by the then Soviet Union in 1958, President D. Eisenhower of the USA set up the Advanced Projects Research Agency (ARPA) in an effort to regain the world lead position in science and technology. As the cold war deepened, ARPA was tasked by the US Air Force to develop a system that would enable 'control and command of the military and missiles to survive a nuclear attack'. They assigned this project to 'civilians' at America's top universities who developed the Internet in 1969. But just as ultrasound, Teflon and other 'military' inventions found their way into every day medical use, so too has the Internet. However, no other technology to date has had as great an impact on medicine and society. It has revolutionized the ways in which we may learn and practise our art.

Communication

For most civilians, the revolution started with electronic mail (e-mail). As the cost impediment has disappeared, this method of communication has become widely available. Indeed, times have moved on since Oyston's[1] online worldwide survey in 1997 showed that mainly male American doctors in university hospitals were using e-mail. It is now the key method of personal communication. Most professional and official communications also take this form. International correspondence is easily and cheaply achieved via e-mail. The *British Journal of Anaesthesia* and most other anaesthetic journals allow the submission of articles for publication via e-mail, although a signed letter is still required for copyright reasons. Some anaesthetic departments now distribute rotas and memoranda via e-mail.

More directly, interactive methods of communication have also been developed. In 1993, Ruskin and Tissot[2] reported online case conferencing. In 1994, Ruskin and colleagues set up a worldwide anaesthetic forum,[3] which has evolved into one of the premiere anaesthetic websites (Gasnet, http://www.gasnet.org). These days, case conferencing can easily occur at an international level, utilizing software such as NetMeeting (©Microsoft Corporation, Seattle, WA, USA) that allows both instant voice and video communication with the option of sharing files and data at the same time.

Another method of communication is via the bulletin board. Participants can post their opinions on a subject matter online and, thus an informal discussion may ensue. Indeed, Mentzer and colleagues[4] extolled Ruskin's bulletin board as a paradigm of the 'Global department of anaesthesia', allowing the exchange of opinions and sharing of ideas about areas of controversy in anaesthesia.

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World Wide Web

This was developed by CERN (European Organisation for Nuclear Research) in Switzerland and was made available to the public by the WWW Consortium in 1992. A standard protocol (hypertext transfer protocol—HTTP) allows computers to log on and upload/download files for display and use from another computer (known as a server). Most websites have gone beyond the rudimentary page merely providing contact details, to sophisticated web pages that provide a multimedia experience.

A multitude of anaesthetic websites has been published in the last few years. A web search using the key words 'Anaesthesia' and 'United Kingdom' using the Google search engine (http://www.google.com) revealed 14 514 web pages. They take many forms and shapes. Some belong to professional organizations and associations (these formed the majority of the top 100 hits from the search). These mainly provide information about the activities of the various groups. The Association of Anaesthetists of Great Britain and Ireland (http://www.aagbi.org) and the Royal College of Anaesthetists (http://www.rcoa.ac.uk) have such websites. There are also non-affiliated websites that provide anaesthetic information as either a collection of references or as chapters of an electronic textbook. Some of the better-known anaesthetic websites include the Global Anaesthetic Server GASNet (http://www.gasnet.org), the Virtual Textbook of Anaesthesia (http://www.vitual-anaesthesia-textbook.com), and the Oxford Pain Website (http://www.jr2.ox.ac.uk/Bandolier/painrej/painpag/index.html). They provide a wide breadth and depth of information to satisfy the needs of trainees and consultants. Other websites such as the New York School of Regional Anesthesia (http://www.nysora.com) lead the way in utilizing the web. This site contains well-described text and diagrammatic annotations, and streaming video demonstrations of regional blocks. Another category of anaesthetic website is the Patient Information site. Some professional organisations provide 'Patient Information' subsections on their websites (http://www.rcoa.ac.uk/public.html), but there are a significant number of websites that are based on individual accounts by patients who have undergone anaesthesia.

Many would agree that one of the most important features of the World Wide Web is the medical search engine. Foremost is the American National Health Library's Medline.[5] Initially limited to collections of abstracts on proprietary CD-ROMs that could be searched using MeSH (Medical Subject Headings), this system involved hours spent in the library sifting through CD-ROMs. However, with the advent of the Internet, the National Library for Health publicized its catalogue online, allowing free access to anyone. Now one may perform a Medline search either on PubMed (http://www.ncbi.nlm.nih.gov/PubMed), or many other combinations and permutations of the medical search engine. The NHS is in the process of setting up its own online national electronic medical library (http://www.nelh.nhs.uk).

What has made things more exciting for the speciality is the fact that anaesthetic journals are now going online and are establishing searchable electronic archives. One can look up subjects of interest and get the full articles while online. For example, the *British Journal of Anaesthesia* (http://www.bja.oupjournals.org) is available online with full text accessible to all journal subscribers. However, not every journal provides free access to full articles. Some institutes, within the confines of copyright law, will allow their employees to have online access to full articles of journals that they keep in their libraries.

More exciting developments such as the development of web-based live databases of patients with difficult airways,[6] and individuals susceptible to malignant hyperthermia,[7] only serve to reinforce the versatility and potential of the web.

Problems for anaesthetists

Quality assurance

As medicine moves into a new era of evidence-based practice, it is important that our common sources of information have statements based on facts. Journals have struggled for a long time to ensure that only quality material is published. One of the strongest methods of ensuring quality in print journals is through the peer-review system. The standards that have taken so many years to attain in print should be applied to the web as well. Many authors in recent times have worried about how the great potential of the Internet may be lost due to the apparent abundance of dubious medical information.[8–10] Anaesthetists have several options to rate the credibility of web sites.

Professional organization endorsement is one method. For example, both the Association of Anaesthetists and the Royal College of Anaesthetists have links pages on their websites. While not directly responsible for the content of the web sites listed on these pages, in general, both professional bodies by implication are happy for their members to obtain information from these websites. A further extension of this practice is to have independent body adjudication of web site content with subsequent award of a credit rating. Med411.com and Health on the Net (http://www.hon.ch/home.html) are examples of such organizations.

Peer review is a tried and tested method that can easily be extended to the Web. Some organizations already have this method of quality assurance in place, for example, the Virtual Textbook of Anaesthesia. Other websites attain credibility by clearly stating the qualifications of the authors. The World Federation of Anaesthetists follows this model and has a very successful website (http://www.nda.ox.ac.uk/wfsa) that is designed to provide updated information for anaesthetists in developing countries.[11]

There are counter arguments to all these strategies for quality control. Following Shapira and colleagues[12] concerns about use of web-based resources as revision material by residents, Allen[13] questioned the objectivity of peer review by stating that 'authors tend to support their own opinions'. He advocated the process of critical appraisal, encouraging authors to explain how the literature search was performed, why individual articles were utilized, and how areas of disagreement were dealt with. He suggests critical appraisal is a valuable tool that should be implemented in the authoring of medical websites.

Copyright matters

The question of intellectual property is a difficult one. While it is quite reasonable to argue for copyright protection, some are of the opinion that copyrighting *academic* material has the negative effect of increasing the cost of access to these materials. This only worsens the plight of those with less financial resources. Some organizations have started to tackle this particular problem. Academic powerhouses such as the Massachusetts Institute of Technology (http://web.mit.edu/) have taken the bold and unprecedented step of putting all their course material online without any restriction but still retaining copyright. The World Federation of Societies of Anaesthetists (WFSA) has placed material online with the specific goal of reaching many anaesthetists in the third world who have less access to costly print journals (http://www.nda.ox.ac.uk/wfsa/index.html).

Some rightly argue that authors have worked hard in preparing their material for publication and should receive recognition for it. Furthermore, their material should not be plagiarized for material gain. Others would argue that in academic circles the only true goal of any academic publication is to enhance knowledge. The only people who would gain from having this knowledge are practising anaesthetists. Should this information and knowledge be protected from free distribution? Currently some academic journals charge for a reprint of a single article. For example, those journals published by Blackwell Science and Munskaard (http://www.Blackwell-synergy.com) charge US$16.00 for a reprint of any of their articles. However, others, such as the *British Medical Journal* (http://www.bmj.com), provide a free-for-all online archive of all their journals since 1994. The *British Journal of Anaesthesia* is currently between the two extremes, allowing full online access to its archive to subscribers of the print journal. A number of anaesthetic trainees (usually around the time of their examinations) have compiled anaesthetic databases for use on handheld computers, and most have made these free to download from the Internet. This is a trend that will continue into the future. We would welcome other anaesthetic journals contemplating these bold new steps.

Security

As with most things in life, there is a downside to this wonderful technology. While the lack of a control structure has been its strength, in some instances it is also its Achilles' heel. There is an ever-present worry of a hacker 'attacking' a site and altering the site content or worse, gaining access to confidential patient information.

Many suggestions have been put forward regarding Internet security. Some organizations with high-value data use intranets to allow only a select group of individuals to have access to their information. These take the form of local area networks. Most NHS trusts in the UK have such set-ups. Trust policies, guidelines, protocols, and databases can be posted on a website limited to an intranet. For information that is designed to have a national or a worldwide audience, firewalls have tended to be used to help protect the integrity of the published data/text. Data encryption is now becoming a well-recognized method of protecting information submitted on the Internet as well as by electronic mail.[14] Digital signatures can combine with encryption to improve security.

Despite all these potential problems, the Internet remains a wonderful invention with a great future. It is a testimony to the potential of the Internet that most of us have been presented with information obtained from the web by our patients. Sometimes we have to be wary of these 'facts' and warn our patients that a little knowledge may be dangerous. But we all should welcome this information revolution. Patient empowerment is important for the patient and the practitioner. Without appearing to be paternalistic, there are ways of directing patients to credible websites. These include our professional organizations' websites as well as those that belong to our individual institutions. The web addresses can easily be placed on anaesthetic information leaflets that patients receive at pre-clerking.

We need to encourage surveys and studies in the literature that look at the quality of website contents. It is encouraging to see a few journals featuring reviews of medical websites (e.g. *New England Journal of Medicine*, http://www.nejm.com). We also need to encourage our anaesthetic journals to feature web-related material over and above the few articles that have been published in recent years.[15–19] The authors would welcome monthly or bi-monthly reviews of websites.

The future

The authors envisage an anaesthetist's operating list for next week being delivered by e-mail together with an attachment detailing anaesthetic pre-assessment pro-formas, filled in by the surgical house officer at pre-assessment clinic. Results of any tests performed including high-definition images of x-rays, CT scans and ECGs would be included. Red-flag conditions such as malignant hyperthermia or rare medical syndromes would have resulted in an automatic request being sent to the medical records department so that the patient's notes could be delivered, in advance, to the anaesthetist for perusal. Prior to departing on an inter-hospital transfer, the anaesthetist could send an electronic file with all relevant information to the receiving consultant. This allows a full appraisal of the patient and preparation for his/her arrival.

The patient who is preparing to come into hospital prior to a major operation can log on to the hospital website and select the anaesthesia section. Here he/she finds out information about what to expect during a general anaesthetic. The patient is comforted by the experiences of previous patients who have published their opinions on this website. He/she is also able to access information for patients on the Royal College of Anaesthetists website (http://www.rcoa.ac.uk/public.html).

The trainee gets home after a day at work. He/she checks their e-mail to see what delights next week's duty roster holds. The trainee then logs on to *British Journal of Anaesthesia* online (http://www.bja.oupjournals.org) to review the article that was being discussed earlier in the day with his consultant. The trainee checks availability and books a place on an examination revision course online. Finally, he/she spends half an hour doing practise MCQs online (e.g. http://www.anaesthesiauk.com) before eventually logging off.

All of us can see that this future fantastic is just round the corner. We must continue to keep pushing the boundaries and maintain our reputation as the speciality at the cutting edge of technology.

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CLINICAL INVESTIGATIONS

Use of a high-fidelity simulator to develop testing of the technical performance of novice anaesthetists†

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Background. We used the Delphi technique to gain a consensus from 26 consultant anaesthetists about technical tasks during general anaesthesia. We then developed a technical scoring system to assess anaesthetists undertaking general anaesthesia with rapid sequence induction.

Methods. We then followed the performance of six novice anaesthetists on five occasions during their first 3 months of training. At each, visit each novice 'anaesthetized' the Human Patient Simulator at Bristol Medical Simulator Centre. For comparison seven post-fellowship anaesthetists were scored on one occasion.

Results. Novice scores improved significantly over the 12-week period ($P<0.01$). A significant difference was also found between the final novice scores and the post-fellowship subjects ($P<0.05$).

Conclusions. These findings suggest that simulation can be used to observe and quantify technical performance.

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A 'comprehensive anaesthesia simulation environment'[1] is a useful place in which to assess many aspects of anaesthetists' performance. It is a realistic environment where conditions can be simulated to match the needs of the assessment.

Researchers using this simulated operating theatre environment have developed objective scoring systems for both technical and behavioural performance during critical incidents.[2 3] We are not aware of any simulator-based performance studies that observe routine anaesthesia or track individuals' progress over time. To use the simulation suite to assess anaesthetic trainees, we should develop and validate a scoring system and an appropriate simulation environment.

We set out to: (1) develop an appropriate validated scoring system for technical performance of individual anaesthetists undertaking general anaesthesia with rapid sequence induction; (2) see if the expected improvement in technical performance of novice anaesthetists in their first 3 months could be observed in the simulation suite and quantified using the scoring system.

Methods

Development of a technical scoring system using the Delphi technique

The conventional Delphi technique was used to obtain a consensus view on a subject from a group of experts.[4] We identified 28 consultant anaesthetists in our region with an interest in training as an 'expert' group and invited them by letter to take part in the study. Each anaesthetist was given the opportunity to decline.

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†This article is accompanied by Editorial I

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Table 1 Tasks and associated mean scores from the first and second rounds of Delphi The final weighted whole number 'score' for each task is also shown

Task	1st	2nd	Score
Check anaesthetic machine			
Calibrate inspired oxygen and attach	4.3	4.4	4
Tug test all pipelines	4.2	4.2	4
Ensure oxygen supply attached	4.9	4.9	5
Spare oxygen cylinder attached	4.8	4.8	5
Check adequate supply of other gases (nitrous oxide air, carbon dioxide)	3.6	3.6	4
Pressure gauges each 400 kPa	4.2	4.3	4
Check operation of all flow meters	4.6	4.5	5
Oxygen flowmeter only at 5 litre min^{-1} reads 100% inspired oxygen	4.4	4.4	4
Turn off all flowmeters (after previous checks)	4.1	4	4
Check emergency oxygen flush	4.9	4.7	5
Check vaporizers			
Correct mounting	4.8	4.7	5
Correct filling	4.6	4.6	5
Turn on vaporizer—check for leaks	4.8	4.8	5
Turn off vaporizer—check for leaks	4.5	4.5	5
Check breathing system			
Configuration	4.9	4.9	5
Reservoir bag and expiratory valve	4.9	4.9	5
Check for leaks	4.9	4.9	5
Check ventilator	4.5	4.5	5
Check suction	4.9	4.9	5
Check equipment			
Two laryngoscopes—bulbs working	4.8	4.8	5
Tracheal cuff	4.7	4.7	5
Mask attached to circuit	4.4	4.5	5
Self inflating bag available	4	3.9	4
Bougie available	4.9	4.9	5
Drugs drawn up pre-induction			
Suxamethonium	5	5	5
Atropine	4.8	4.8	5
Induction agent	5	5	5
Opioid	3.7	3.7	4
Relaxant	3.7	3.7	4
On patient arrival (before induction)			
Talk to patient	4.7	4.7	5
Check tipping trolley	4.8	4.8	5
Optimize head position	4.4	4.5	5
Check notes and consent	4.2	4.3	4
Anaesthetist wearing gloves	3.1	3.1	3
Check surgeon available before induction	4.2	4.3	4
Monitoring before induction			
ECG	4.3	4.3	4
Pulse oximetry	5	5	5
Capnography	3.4	3.4	3
Inspired oxygen	3.7	3.6	4
Non-invasive arterial pressure	4.3	4.3	4
Induction			
Cannula sited and patent	5	5	5
Free running drip	3.5	3.5	4
Suction under pillow	5	5	5
Pre-oxygenate with close fitting mask	5	5	5
Induction (continued)			
Pre-oxygenate time (3 min by clock)	4	4.1	4
Check assistant understands and can give cricoid pressure	4.9	4.9	5
Cricoid pressure—hand in place before any drugs given	3.6	3.6	4
Induction drugs given	5	5	5
Correct dose (propofol 1.5–2.5 mg kg^{-1} thiopentone 2–4 mg kg^{-1})	4.7	4.7	5
Suxamethonium	5	5	5
Correct dose (1–1.5 mg kg^{-1})	5	4.9	5
Evidence of relaxation before intubation (e.g. fasciculations fading)	4.4	4.4	4
Check tube position—auscultate	4.5	4.5	5
Check tube—capnography	4.5	4.5	5
Remove cricoid pressure only once tube position checked	5	4.9	5
Secure tube	4.6	4.6	5
Hand ventilate with volatile before attaching to ventilator	4.1	4	4
Evidence of NM function before more relaxant (PNS or clinical)	3.1	3.1	3
Relaxant given	3.9	3.9	4
Correct dose (atracurium 0.5 mg kg^{-1}, vecuronium 0.1 mg kg^{-1})	4.1	4.1	4
Appropriate analgesia before incision (morphine 0.1–0.15 mg kg^{-1}, fentanyl 1–2 μg kg^{-1}, alfentanil 10–20 μg kg^{-1})	4.4	4.3	4
Patient inspection (following induction)			
Check chest movement	4.8	4.8	5
Feel pulse	4.1	4.1	4
Check pressure points/position	4.2	4.2	4
Eyes taped shut	4.1	4	4
Appropriate goals for anaesthetists			
Inspired oxygen >30%	4.5	4.5	5
Summate MAC >1%	4.1	4	4
Systolic 80–140 mm Hg	4.1	4	4
Heart rate 50–110 beats min^{-1}	4	4	4
Sp_{O_2} >95%	4.6	4.5	5
End-tidal carbon dioxide 30–40 mm Hg	4.1	4.1	4
Intraoperative checks			
Surgical site observed and discussed with surgeon	3.6	3.6	4
Fluids given appropriately	4.4	4.4	4
Write chart	4.1	4.2	4
Extubation			
Vaporizer off	4.2	4.3	4
Neuromuscular function assessed with PNS	3.1	3.1	3
Reversal given if evidence of residual block	4.8	4.8	5
Dose (neostigmine 2.5 mg, atropine 0.6 mg, glycopyronnium 0.5 mg)	4.5	4.5	5
Pharyngeal suction	4.9	4.8	5
100% oxygen via ventilator	4.7	4.7	5
Ventilator off once spontaneous respiration returned	4.4	4.4	4
Lateral position before extubation	4.5	4.5	5
Patient awake before extubation	4	4	4
100% oxygen via breathing circuit once extubated	4.4	4.4	4
Confirm airway patent, breathing and pulse present before transfer	4.9	4.9	5
Postoperative management			
Communication with recovery staff description of:			
Patient pre-morbid status	4.6	4.6	5
Operative procedure	4.8	4.8	5
Instructions for postoperative care	4.9	4.9	5
Analgesia prescribed	4.7	4.7	5
Oxygen given via Hudson mask	4.5	4.5	5
Fluids prescribed	4.6	4.5	5

A list was made of the technical tasks undertaken during rapid sequence induction and maintenance of general anaesthesia. This list was based on observed practice, textbook descriptions, and guidelines issued by the Association of Anaesthetists.[5] The original list of tasks was formulated into a scoring sheet with room for comment.

The scoring sheet was sent to the participants who were invited to comment about the inclusion of each task and rank its relative importance on a scale of 1–5. They were asked to add tasks to the list that they felt were important and had been omitted. The scoring sheet was returned to us. The results were analysed to obtain a mean score for each task. The mean scores and additional tasks were noted on the scoring sheet to produce a new modified scoring sheet.

The review process was repeated. Each participant was sent a copy of the new modified scoring sheet and a copy of their own original scores. They were asked to review their original response against the mean value derived from the group opinion and modify their response if they felt it was appropriate. To comply with the conventional Delphi technique the review process had to be done at least once. The additional items were reviewed separately for a second and final time in order to comply with the Delphi process.

The forms were processed through a central office and results analysed using Microsoft Excel. The anonymity of the participants was preserved with a numerical identifier.

Results of scoring system development

Twenty-eight consultant anaesthetists were approached to take part in the study. Twenty-six agreed to do so.

The list of tasks with associated group mean scores from the first and second surveys and the final weighted scores (whole number) are shown in Table 1. The 19 additional items, their relevant mean scores for two rounds, and final weighted scores are shown in Table 2. We stopped the Delphi process after two rounds.

Table 2 Additional tasks added by respondents after the first Delphi round First and second round scores plus final weighted score for each item are shown

Task	1st	2nd	Score
Preoperative assessment			
Full anaesthetic history	4.6	4.6	5
Assessment of airway including dentition	4.8	4.8	5
Assessment of adequacy of resuscitation	4.8	4.8	5
Pre-medication with citrate/ranitidine (obstetrics)	4.8	4.6	5
Preoperative equipment check to include:			
Ready availability of difficult intubation kit	4.7	4.9	5
Ready availability of emergency drug kit	4.5	4.4	4
Defibrillator available	4.5	4.4	4
Second assistant available in the room if ODA doing cricoid	4.3	4.2	4
Before induction			
Discusses and confirms procedure with surgeon	4.4	4.2	4
Lateral tilt (obstetrics)	4.9	4.8	5
Suck out NG tube	4.5	4.5	5
Intraoperative checks			
Antibiotic prophylaxis	3.8	3.6	4
Antithrombotic precautions	3.9	3.7	4
HME filter	3	2.9	3
Warming blanket/thermal drapes	3.7	3.6	4
Postoperative management			
Correct positioning in recovery	4.4	4.6	5
Criteria for discharge from recovery stated	4.3	4.2	4
Early determination of postoperative destination e.g. ITU	4.5	4.3	4
Airway assessment			
Check neck mobility	5	4.8	5
Check mouth opening	5	4.9	5

Methods used to observe technical performance

This part of the study was approved by the Local Ethics Committee and conducted at the Bristol Medical Simulation Centre. This contains a high-fidelity Human Patient Simulator produced by Medical Education Technology Inc. This is kept in a realistic operating theatre environment, complete with anaesthetic machine, simple and invasive monitoring, and a full array of anaesthetic and surgical equipment. Two cameras and microphones discreetly placed in the operating theatre are used for recording the events onto videotape.

We recruited six novice anaesthetists from four different hospitals in the South West. We brought them to the centre on five separate occasions, at the end of weeks 1, 2, 4, 8, and 12 of their training. On each visit the novices were given a different 'patient' to anaesthetize on their own. They received the scenarios in the same order and each of the scenarios was designed to prompt the anaesthetist to plan a general anaesthetic with rapid sequence induction. On their first visit to the centre each novice was given a brief introduction to the simulation environment primarily to explain the features of the simulator.

The patient simulator can be programmed to represent patients with different baseline physiological conditions. These simulated patients can be created repeatedly. For

Table 3 Summary details of the simulated patient for each study week

	Patient	Diagnosis	Operation	General health	Other relevant history
Week 1	Male 18 yr, 70 kg	Appendicitis	Appendicectomy	ASA I	Dental anaesthesia in past—no problems
Week 2	Female 22 yr, 65 kg	Ectopic pregnancy	Laparoscopy	ASA I	Dental anaesthesia—no problems
Week 4	Female 18 yr, 65 kg	Compound fracture radius and ulnar	Internal fixation	ASA I	Gynae op—no problems
Week 8	Male 20 yr, 70 kg	Possible appendicitis	Laparoscopy? Proceed	ASA I	Previous anaesthetic OK
Week 12	Female 18 yr, 65 kg	Possible ectopic pregnancy	Laparoscopy	ASA I	Active oesophageal reflux

Table 4 Week 1 and week 2 technical scores, mean and SD, for the six novices by two raters

Novice	Week 1		Week 2	
	Rater 1	Rater 2	Rater 1	Rater 2
1	65	59	187	205
2	14	14	258	254
3	25	20	277	261
4	133	140	210	210
5	72	82	195	175
6	133	128	223	213
Mean (SD)	74 (51)	73 (53)	225 (36)	219 (32)

this study all the simulated patients were programmed as 'standard man' a fit 70-kg man. However, the patient details presented to the anaesthetist (gender, presenting complaint, medical history, and the planned operation) varied from visit to visit and are summarized in Table 3.

The theatre set-up was the same in each scenario:

1. the anaesthetist was told it was the first case on a Monday morning list and the theatre had not been in use over the weekend;
2. the form indicating consent for operation was absent from the notes but was available in a nearby office;
3. it was not apparent that the surgeon was in the theatre suite at the start of the case.

Thus, the anaesthetist was expected to check the equipment, find the form showing patient consent and contact the surgeon before starting the anaesthetic.

An anaesthetic assistant (a trainer in the simulator centre) was available to help with preparation and conduct of anaesthesia. The trainee could also ask further questions of the simulated patient. Once the anaesthetic was underway, the surgical procedure was acted out by members of the research team. The novice was expected to continue anaesthesia until the end of surgery, wake the patient up, and then hand over to recovery staff. The trainees were *not* debriefed on their performance during the study.

Each novice was videotaped for the whole procedure. Videotape captured the action in the theatre suite as well as an inset display showing the monitored physiological variables. Performance was scored from videotape rather than from the trainees direct actions using the Delphi derived technical scoring system described above. For this study we used the tasks listed in Table 1. All videos were analysed separately by two raters.

In addition to the novice anaesthetists, we recruited seven post-fellowship anaesthetists to the study. They were asked to anaesthetize a single case (week 1 patient, Table 3). This patient was presented in an identical fashion. Each of the anaesthetists was videotaped and scored by the two raters.

Finally, to assess the reliability of the scoring system, five consultant anaesthetists (not involved with the study) who were familiar with the simulation suite were asked to rate one videotape. They were given a brief verbal introduction to the use of the technical scoring system and then scored Novice 2 (week 12 tape).

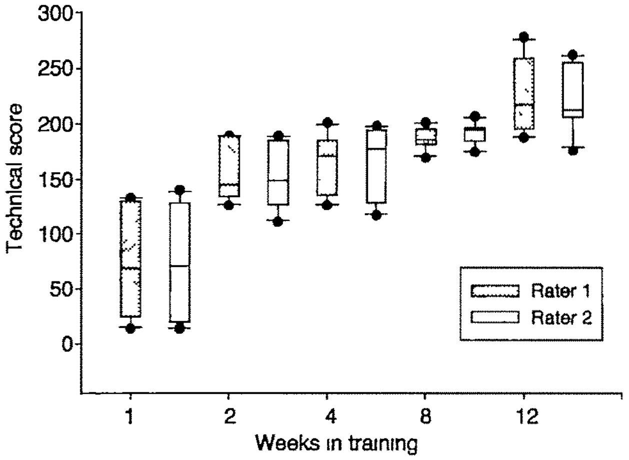

Fig 1 Plots showing technical scores awarded by two raters at each of five visits during the first 12 weeks of training. Each box represents interquartile range for six subjects, the whiskers represent 10th and 90th percentiles. The median is shown within the box and the full range of scores represented by the dots.

Results of performance assessment

The scores attributed by the two raters for each novice at the first and last visit are shown in Table 4. The scores on each visit for each of the six novices are plotted in Figure 1. Because the null hypothesis was no *increase* in score over the training period, one-tailed, paired *t*-tests for the scores at the first and last visit (weeks 1 and 12 of training) were performed on the data from each rater. Both sets of data showed a significant difference $P<0.01$ (rater 1, $P=0.002$; rater 2, $P=0.003$) with the week 12 scores higher than the week 1 scores.

Both raters scored the post-fellowship group. Table 5 shows the scores from each rater and the experience of each anaesthetist at the time of testing. Because the null hypothesis was no *difference* between the two groups, two-tailed, non-paired *t*-tests comparing novice scores at week 12 and the scores from the post-fellowship group for both raters were performed. These showed a significant difference $P<0.05$ (rater 1, $P=0.03$; rater 2, $P=0.01$).

The scoring patterns from five raters reviewing novice 2 are shown in Table 6. This shows the degree of agreement between raters on whether or not they did or did not see the novice performing an action. There was complete agreement on 62 out of 91 actions (68.1%) and four out of five raters agreed on 80 out of 91 actions (88%). Technical scores were calculated for each of the five raters (rater 3=265, rater 4=284, rater 5=305, rater 6=270, and rater 7=273). The standard deviation (SD) of these scores is 16. The SD for all novice 2 scores between week 1 and 12 is 92 (rater 1) and 93

Table 5 Technical scores for experienced anaesthetists *Indicates previous simulator experience

Expert	Score-rater 1	Score-rater 2	Experience
1	278	275	SpR 4
2*	285	275	SpR 4
3	281	276	SpR 4
4	313	309	SpR 4
5*	288	283	Consultant >10 yr
6	296	293	Consultant > 1 yr
7	272	265	SpR 4

(rater 2). The SD of *all* six novices scores at week 1 is 51 (rater 1) and 53 (rater 2); at week 12 this SD falls to 36 (rater 1) and 32 (rater 2).

Discussion

An anaesthetist's actions in the operating theatre can be broadly divided into technical and non-technical components. In order to validate the simulation suite as an environment for assessing the technical aspects of performance, we needed to show that different performance abilities could be measured using a valid scoring system. We hypothesized that it would be easiest to demonstrate changes in technical performance in a short period of time in novice anaesthetists. We therefore developed a scenario of general anaesthesia with rapid sequence induction, which requires the individual to follow a series of prescribed technical steps (especially at induction and extubation). All SHOs must be familiar with this technique by the time they have to provide anaesthesia with limited supervision (usually after 3 months of training).

The Delphi technique and scoring system

We wanted a scoring system that would be valid and reliable. Previously described tests of skills[6] or technical ability, specific[2] or non-specific[7] to the simulator were not suitable for scoring this scenario. The problems relating to methods of assessment used in simulation have recently been reviewed by Byrne and Greaves.[8] They concluded that of 13 publications relating to assessment of performance only four had paid attention to investigating the validity and reliability of the assessment system.

To address some of the issues of validity we chose the Delphi technique to develop our scoring system. Delphi has not been widely used in medicine but it has been used to describe pointers of diagnosis in malignant hyperpyrexia[9] and to define necessary skills for pre-registration trainee doctors.[10] Using Delphi we would gain a consensus expert opinion (important in rapid sequence induction of anaesthesia which has been shown to be open to individual interpretation[11]) and the tasks would have scores ranked for importance. Thus, we hoped the scoring system applied to this one scenario would have construct validity.[12]

The Delphi process is cumbersome to perform. We satisfied convention by recruiting a panel with 15–30 'experts'. We felt that a group of consultant anaesthetists with responsibility for training had sufficient experience in rapid sequence induction to be considered 'expert'. Although three or four round processes are encouraged to achieve maximum input from experts we ended the study after two rounds because:

- mean scores were rounded up ($\geq$0.5) and only one out of 92 items would have changed final allotted scores between the first and second rounds;
- the task list was extremely long and respondents needed to remain motivated to complete it;
- motivation seemed good on the first round as we had useful feedback and comment, which became less on the second round.

We used mean rather than median scores as a measure of central tendency and for feedback to the group. We reviewed the difference between mean and median scores for the second round data and found no difference.

The results of the novice study suggest that the scoring system is valid as we demonstrated that the technical scores of all the novices improved with time (Fig. 1). Also, the expert group (only two of whom had prior simulator experience) performed better than novices after 3 months of training.

A scoring system should have good inter-rater reliability if it is to be used for a trainee assessment programme. Many performance studies in simulators have been criticized for failing to address this issue.[8] Gaba found better inter-rater reliability with technical rather than behavioural rating.[2] We would also expect good inter-rater reliability on a checklist scoring system where actions are either present or absent and videotape can be reviewed if concentration is lost or clarity required. Our scores from two raters look similar but might be criticized because the ranking of novices differs slightly between raters. Rater 1 consistently scored higher than rater 2. The actual difference in scores was small and equivalent to the value of two or three items off the checklist.

To study inter-rater reliability further we asked five raters who had never used the scoring system before to score one tape after minimal tuition. Agreement was good especially if a consensus was taken (i.e. four out of five raters). However, this makes no allowance for the influence of chance. We therefore calculated the actual technical scores generated by the five raters, which ranged from 265 to 305 with a SD of 16 (the equivalent to three or four items on the scoring system).

When we compare this to the results generated by rater 1 and rater 2 scoring the six novices at week 1, we find that the SD for the novices are similar for both raters (51 and 53) but markedly greater than the SD of the single video rated by the five raters. This suggests that rater 1 and rater 2 found differences amongst the novices at week 1, which were unlikely to be simply the result of rater error. At week 12, the SD amongst the six novices were smaller (35 for rater 1;

Table 6 Presence (1) or absence (0) of items by five new raters of one videotape

Activity	Rater 3	Rater 4	Rater 5	Rater 6	Rater 7
Check anaesthetic machine					
Calibrate inspired oxygen and attach	0	0	0	0	0
Tug test all pipelines	0	0	0	0	1
Ensure oxygen supply attached	1	1	1	1	1
Spare oxygen cylinder attached	1	1	1	1	1
Check adequate supply of other gases (nitrous oxide, air, carbon dioxide)	1	1	1	0	1
Pressure gauges each 400 kPa	0	0	0	0	0
Check operation of all flowmeters	0	1	1	0	1
Oxygen flowmeter only at 5 litre min^{-1} reads 100% inspired oxygen	0	0	1	0	0
Turn off all flow meters (after previous checks)	0	1	1	1	0
Check emergency oxygen flush	0	0	0	0	0
Check vaporizers					
Correct mounting	1	1	1	0	1
Correct filling	0	0	1	0	0
Turn on vaporizer—check for leaks	0	0	1	0	0
Turn off vaporizer—check for leaks	0	1	1	0	0
Check breathing system					
Configuration	1	0	1	1	1
Reservoir bag and expiratory valve	0	1	1	1	1
Check for leaks	1	1	1	1	1
Check ventilator	1	1	1	1	1
Check suction	1	1	1	1	1
Check equipment					
Two laryngoscopes—bulbs working	1	1	1	1	1
Tracheal cuff	0	1	0	0	0
Mask attached to circuit	1	1	1	1	0
Self inflating bag available	0	0	0	0	0
Bougie available	0	0	0	0	0
Drugs drawn up pre-induction					
Suxamethonium	1	1	1	1	1
Atropine	1	1	1	1	1
Induction agent	1	1	1	1	1
Opioid	1	1	1	1	1
Relaxant	1	1	1	1	1
On patient arrival (before induction)					
Talk to patient	1	1	1	1	1
Check tipping trolley	1	1	0	0	0
Optimize head position	0	0	0	0	0
Check notes and consent	0	0	1	1	1
Anaesthetist wearing gloves	0	0	0	0	0
Check surgeon available before induction	0	0	0	0	0
Monitoring before induction					
ECG	1	1	1	1	1
Pulse oximetry	1	1	1	1	1
Capnography	1	1	1	1	1
Inspired oxygen	0	0	0	0	0
Non-invasive arterial pressure	1	1	1	1	1
Induction					
Cannula sited and patent	0	0	0	0	0
Free running drip	0	0	0	0	0
Suction under pillow	1	1	0	0	1
Pre-oxygenate with close fitting mask	1	1	1	1	11
Pre-oxygenate time (3 min by clock)	0	0	1	1	1
Check assistant understands and can give cricoid pressure	1	1	1	1	0
Cricoid pressure—hand in place before any drugs given	0	0	0	0	0
Induction drugs given	1	1	1	1	1
Correct dose (propofol 1.5–2.5 mg kg^{-1}, thiopentone 2–4 mg kg^{-1})	0	0	0	1	0
Suxamethonium	1	1	1	1	0
Correct dose (1–1.5 mg kg^{-1})	1	1	1	1	0
Evidence of relaxation before intubation (e.g. fasciculations fading)	1	1	1	1	1
Check tube position—auscultate	1	1	1	1	1
Check tube—capnography	1	1	1	1	1
Remove cricoid pressure only once tube position checked	1	1	1	1	1
Secure tube	1	1	1	1	1
Hand ventilate with volatile before attaching to ventilator	1	1	1	1	1
Evidence of NM function function before more relaxant (PNS or clinical)	1	1	1	1	1
Relaxant given	1	1	1	0	1
Correct dose (atracurium 0.5 mg kg^{-1}, vecuronium 0.1 mg kg^{-1})	1	1	1	0	1
Appropriate analgesia before incision (morphine 0.1–0.15 mg kg^{-1}, fentanyl 1–2 μg kg^{-1}, alfentanil 10–20 μg kg^{-1})	1	1	1	1	1
Patient inspection (following induction)					
Check chest movement	0	0	0	0	1
Feel pulse	0	0	0	0	0
Check pressure points/position	0	0	0	0	0
Eyes taped shut	0	0	0	0	0
Appropriate goals for anaesthetists					
Inspired oxygen >30%	1	1	1	1	1
Summate MAC >1%	1	1	1	0	1
Systolic 80–140 mm Hg	1	1	1	1	1
Heart rate 50–110 beats min^{-1}	1	1	1	1	1
S_{pO_2} >95%	1	1	1	1	1
End-tidal carbon dioxide 30–40 mm Hg	1	1	1	1	1
Per operative checks					
Surgical site observed and discussed with surgeon	1	1	1	1	1
Fluids given appropriately	1	0	1	1	0
Write chart	1	1	1	1	1
Extubation					
Vaporizer off	1	1	1	1	1
Neuromuscular function assessed with PNS	1	1	1	1	1
Reversal given if evidence of residual block	1	1	1	1	1
Dose (neostigmine 2.5 mg, atropine 0.6 mg, glycopyronnium 0.5 mg)	1	1	1	1	1
Pharyngeal suction	1	1	1	1	1
100% oxygen via ventilator	1	1	1	1	1
Ventilator off once spontaneous respiration returned	1	1	1	1	1
Lateral position before extubation	1	1	1	1	1
Patient awake before extubation	1	1	1	1	1
100% oxygen via breathing circuit once extubated	1	1	1	1	1
Confirm airway patent, breathing and pulse present before transfer	0	0	0	1	0
Postoperative management					
Communication with recovery staff description of:					
Patient pre-morbid status	0	0	1	1	1
Operative procedure	1	1	1	1	1
Instructions for postoperative care	1	1	1	1	1
Analgesia prescribed	1	1	1	1	1
Oxygen given via Hudson mask	0	0	0	0	0
Fluids prescribed	0	1	1	1	1

32 for rater 2). This would be expected if training had enabled those who were less technically competent at the beginning to improve their technical skills. The variation in technical scores within the group at week 12 is still, however, at least twice as great as the variation in the rating of the single video by the five raters. It suggests that even at week 12 individual differences amongst the novices were greater than could be readily accounted for by rater errors.

We conclude that the scoring system is acceptable to a range of experts, can be used with an acceptable level of inter-rater reliability (see above), and it is valid since it detected expected performance differences (see comparisons of week 1 and week 12 and of novices and experts). If simulator tapes were to be used for real assessments and not research, we suggest that two raters might watch each tape together. Our results suggest that they would achieve reasonable levels of agreement. If they discussed any ambiguities as they arose, a sound technical judgement of performance could be achieved. This was obviously not possible as part of a research process.

The novice study

A considerable range of technical scores was noted at the novices' first visit. Although none of the novices had previously held an anaesthetic post, two had worked in Accident and Emergency (novices 5 and 6, Table 4) and one in Intensive Care (novice 3, Table 4). All novices' scores increased, but a higher score in week 1 did not result in a higher score in week 12.

Although we wished to find if different performance abilities could be observed and scored in the simulation environment, we were interested to discover that after 12 weeks the technical ability of the novices was less than the experts. Although it is good that experience leads to continued improvement in technical ability it does lead to the question 'why were novices scoring less well in a set practical task?' Novices scored poorly in machine checking, pre-induction checks and recovery hand-over compared with experts. Only one of the expert group did NOT include checks in their performance. This does raise some interesting questions. Do novices understand that it is their responsibility to check equipment? Do novices know how to check equipment by 3 months? Whose responsibility is it to teach them or have they been taught and not learned it? The Royal College of Anaesthetists have introduced guidelines for the assessment of SHOs in training including a three months assessment, which begins to address these issues.[13]. It is reassuring to note that all the novices in this study understood and employed a rapid sequence induction by the last assessment when they were beginning to undertake emergency cases with limited supervision.

The maximum score possible is 401. The experienced anaesthetists did not score close to the maximum technical score possible (Table 5). This may indicate that the scoring system included aspects of performance that experienced anaesthetists do not include in day-to-day practice. An example of this would be that end-tidal carbon dioxide is used to check for tube placement rather than auscultation of the chest. An alternative explanation is that this may be a feature of providing anaesthesia in a simulation suite. Only one anaesthetist wore gloves in the simulation suite, but we consider that it is highly likely that these anaesthetists would wear gloves for real patients. Further studies comparing simulator and real performance will help to identify differences in practice between the two environments.

We have shown that simulation and a scoring system can document and assess changes in technical performance. Although continued development of valid and reliable scoring systems is necessary, simulation may be a useful tool for assessing trainees during their training. Technical assessments combined with case management analysis could allow standardized competency-based assessment of training to be developed.

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A prospective study of the quality of pre-hospital emergency ventilation in patients with severe head injury

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Background. Pre-hospital endotracheal intubation for the purpose of controlled ventilation may prevent secondary brain injury in patients with severe head injury. In view of the limited monitoring devices utilized in the pre-hospital setting, little is known about the 'quality' of controlled ventilation initiated in the pre-hospital setting.

Methods. Included in this prospective study were 122 trauma patients with severe head injury (abbreviated injury scale score ≥3). In all cases, the pre-hospital treatment included endotracheal intubation in the field. Upon hospital admission, and maintaining the same ventilation mode and setting initiated in the pre-hospital setting, arterial blood gas samples were taken.

Results. 'Optimal' oxygenation (Pa_{O_2} >100 mm Hg) was achieved in 85.2% and 'adequate' ventilation (Pa_{CO_2} 35–45 mm Hg) in 42.6% of the patients upon hospital admission. 'Optimal' oxygenation as well as 'adequate' ventilation was achieved in 37.7% of the study population. Hypoxaemia (Pa_{O_2} <60 mm Hg) was observed in 2.5%, hypercapnia (Pa_{CO_2} >45 mm Hg) in 16.4%, and hypocapnia (Pa_{CO_2} <35 mm Hg) in 40.9% of the study patients. The incidence of hypocapnia was significantly more frequent in polytraumatized patients. Hypocapnia as well as hypercapnia was significantly more frequent in patients with associated pulmonary contusion.

Conclusions. Endotracheal intubation and controlled ventilation of the lungs initiated in the pre-hospital setting do not guarantee optimal oxygenaton and ventilation in patients with severe head injury.

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Independently, but especially in conjunction with hypotension, hypoxaemia and hypocapnia as well as hypercapnia are recognized as major extracranial variables influencing outcome in severely head injured patients.[1 2] Early definitive control of the airway by endotracheal intubation and controlled ventilation should reduce the likelihood of hypoxaemia, hypocapnia, and hypercapnia and may prevent secondary brain injury.[3] Recent studies have demonstrated a significantly improved outcome for patients with severe head injury who were treated with endotracheal intubation and controlled ventilation before transfer to hospital[4–7] Furthermore, when endotracheal inbutation and controlled ventilation was initiated before hospital transfer[8] mortality was significantly reduced in those patients with 'good' compared with those with 'poor' respiratory therapy (25 *vs* 61%). In view of less sophisticated ventilator and the limited ability to monitor oxygenation and ventilation in the pre-hospital setting, the 'quality' of ventilation initiated in the field is uncertain. We studied the effect of endotracheal intubation and artificial ventilation initiated in the field on arterial $P\mathrm{O}_2$ (Pa_{O_2}) and arterial $P\mathrm{CO}_2$ (Pa_{CO_2}) in patients with severe head injury.

Patients and methods

We performed a prospective study of trauma patients with severe head injury admitted to the Federal Armed Forces Medical Center, Ulm—a regional trauma centre—from January 1, 1998, to December 31, 1999. Severe head trauma was defined as head or neck Abbreviated Injury Scale (AIS)[9] score of 3 or more. All patients included in the study had their trachea intubated and ventilation of their lungs controlled in the field with the intention to prevent hypoxaemia as well as hypocapnia and hypercapnia.

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Endotracheal intubation as well as controlled ventilation was conducted according to the current treatment procedure for the Emergency Medical Services of Ulm County, Germany. In this context, immediately after endotracheal intubation the lungs are ventilated using a manually operated ventilation bag (AMBU-Mark III®, Ambu, Friedburg, Germany), connected to an oxygen demand valve (Dräger, Oxydem®, Dräger, Lübeck, Germany), assuring a fraction of inspired oxygen (F_{IO_2}) of 1.0. After the correct position of the tracheal tube is confirmed and secured, further pre-hospital artificial ventilation is maintained automatically by a volume constant portable emergency ventilator (Dräger Oxylog®). The ventilator settings used are a tidal volume of 10 ml kg^{-1} of estimated body weight, respiratory weight of 10 min^{-1} and an F_{IO_2} of 1.0. During pre-hospital treatment, all patients were continuously monitored by pulse oximetry. Upon hospital admission and maintaining the ventilator settings initiated in the field, arterial blood gas samples were taken.

Table 1 Mechanism of injury within the study population

Mechanism of injury	No. (%) of patients
Road accident	92 (75.4)
Home accident	15 (12.2)
Sports accident	8 (6.6)
Homicide/suicide	3 (2.5)
Working accident	4 (3.3)

Recorded data included physical characteristics, mechanism of injury, AIS, Injury Severity Score (ISS)[10], arterial blood gas analysis (pH, base excess, Pa_{O_2}, and Pa_{CO}) upon hospital admission and vital signs upon hospital admission.

All recorded data were collected concurrently and entered into a relational database management system (Microsoft Access, Microsoft Corporation, Redmond, WA, USA) based on the Trauma Registry of the German Society of Trauma Surgery.[11]

'Optimal' oxygenation upon hospital admission was defined as a Pa_{O_2} greater than 100 mm Hg and 'adequate' ventilation as Pa_{CO_2} 35–45 mm Hg; hypoxaemia was defined as a Pa_{O_2} less than 60 mm Hg, hypocapnia as a Pa_{CO_2} less than 35 mm Hg, and hypercapnia as a Pa_{CO_2} greater than 45 mm Hg.[12–14] In order to evaluate the potential influence of age, haemodynamic instability, severe chest injury, or a high injury severity on oxygenation and ventilation, we stratified the study population. Old age was defined as greater than 60 yr of age,[15] haemodynamic instability as a systolic arterial pressure upon hospital admission of less than 90 mm Hg, and severe chest trauma as the presence of pulmonary contusion. Pulmonary contusion was diagnosed by computer tomography, which was conducted on every study patient during the initial in-hospital phase of resuscitation. High injury severity was defined as the presence of polytrauma.[16]

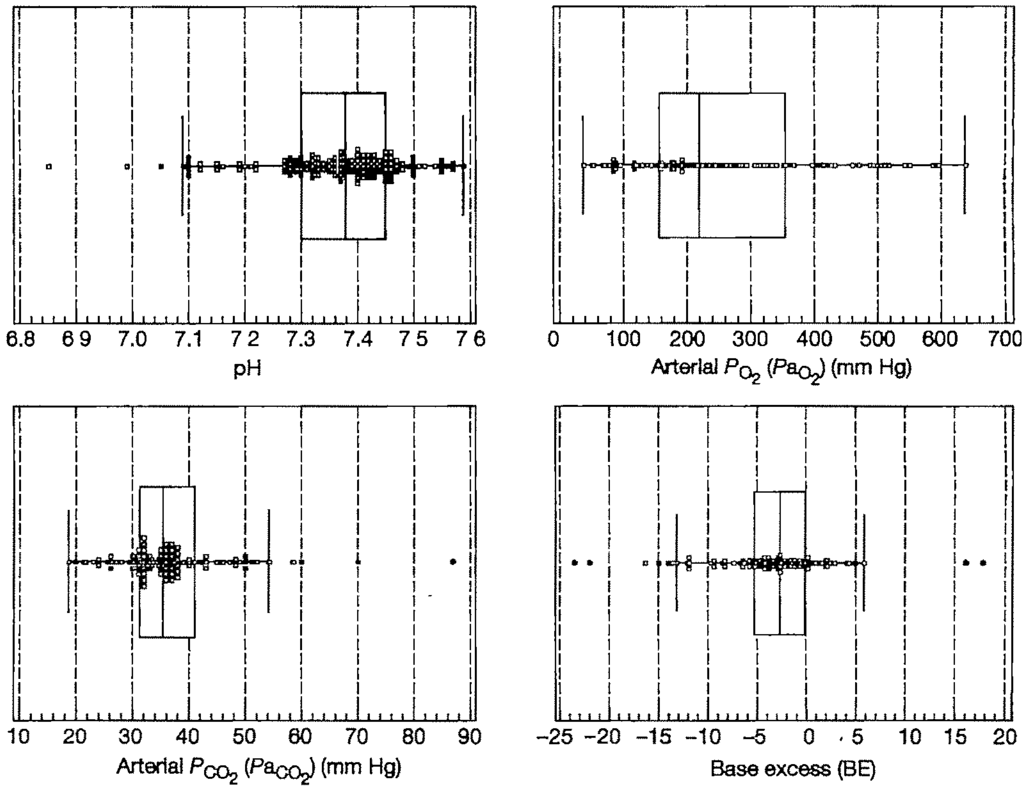

Fig 1 Blood gas analysis within the total study collective (n=122) upon hospital admission (box-and-whisker plots).

Statistical methods

All values in the tables and figures are expressed as mean (SEM) unless otherwise indicated. Each variable was tested for differences between groups by Student's *t* test or chi-squared analysis where appropriate. Statistical significance was set at $P<0.05$. Statistical analysis was performed using specialized statistical software (Almo® version 5.0; K. Holm, University of Graz, Austria).

Results

Out of 127 trauma victims with associated head injury, five patients were excluded from the study, because of failure to obtain an arterial blood gas sample before the ventilator settings were changed upon hospital admission; therefore, 122 trauma patients (93 male, 29 female, age 37 (21) [range 8–89] yr, ISS 25 (15)) were enrolled into the study. All patients sustained blunt trauma; the detailed analysis of the mechanism of the injury is presented in Table 1.

Subsequent patient evaluation and chest radiogram performed upon admission to the hospital confirmed there were no oesophageal or endobronchial intubations. The results of the arterial blood gas analysis (pH, base excess, Pa_{O_2}, and Pa_{CO_2}) upon hospital admission are presented in Figure 1.

In Table 2 the results concerning 'optimal' oxygenation and 'adequate' ventilation in the study population are presented.

'Optimal' oxygenation upon hospital admission was achieved in 85.2% of the study population, 'adequate' ventilation in 42.6% upon hospital admission. Only 37.7% of the study population had been 'optimally' oxygenated as well as 'adequately' ventilated.

The results concerning the incidence of 'non-optimal' oxygenation, hypoxaemia, hypocapnia and hypercapnia within the study population are presented in Table 3.

There were only three cases (2.5% of the total study population) of hypoxaemia upon hospital admission and in all these cases severe extensive pulmonary contusion was present. The majority of the patients with inadequate ventilation upon hospital admission had been hyperventilated (Table 3). The incidence of hypocapnia was significantly more frequent in polytraumatized patients. Hypocapnia as well as hypercapnia was significantly more frequent in patients with associated pulmonary contusion.

Discussion

The pre-hospital phase seems to be the most critical period in determining the ultimate outcome after traumatic brain injury.[17] Critical to the outcome are rapid interventions to prevent secondary brain damage. Fundamental goals of the resuscitation of head injured patients are the restoration of oxygenation and ventilation and the restoration of circulating blood volume and arterial pressure.[18] In this context, various studies[4–7] have demonstrated that endotracheal intubation and controlled ventilation in the field, signifi-

Table 2 'Optimal' oxygenation and 'adequate' ventilation upon hospital admission within the study population (n=122). HI, head injury, SAP, systolic arterial pressure

Group	Optimal oxygenation (Pa_{O_2} >100 mm Hg) (no. (%) of patients)	Adequate ventilation (Pa_{CO_2} 35–45 mm Hg) (no. (%) of patients)	Optimal oxygenation + adequate ventilation (Pa_{O_2} >100 mm Hg + Pa_{CO_2} 35–45 mm Hg) (no. (%) of patients)
Total study population (n=122)	104 (85.2)	52 (42.6)	46 (37.7)
Isolated HI (n=38)	32 (84.2)	16 (42.1)	14 (36.8)
Polytrauma (n=68)	55 (80.9)	31 (45.6)	26 (38.2)
Pulmonary contusion (n=50)	40 (80.0)	20 (40.0)	17 (34.0)
SAP <90 mm Hg (n=9)	7 (77.8)	4 (44.4)	4 (44.4)
Age >60 yr (n=18)	12 (66.7)	7 (38.9)	5 (27.8)

Table 3 Incidence of 'non-optimal' oxygenation, hypoxaemia, hypo- and hypercapnia upon hospital admission within the study population (n=122) HI, head injury, SAP, systolic arterial pressure $^+$Significant at $P<0.05$ by chi-squared test

Group	Hypoxaemia (Pa_{O_2} <60 mm Hg) (no. (%) of patients)	'Non-optimal' oxygenation (Pa_{O_2} 60–100 mm Hg) (no. (%) of patients)	Hypocapnia (Pa_{CO_2} <35 mm Hg) (no. (%) of patients)	Hypercapnia (Pa_{CO_2} >45 mm Hg) (no. (%) of patients)
Total study collective (n=122)	3 (2.5)	15 (12.3)	50 (40.9)	20 (16.4)
Isolated HI (n=38)	0 (0.0)	5 (13.2)	17 (44.7)	2 (5.3)
Polytrauma (n=68)	2 (2.9)	9 (13.2)	21 (30.9)$^+$	14 (20.6)
Pulmonary contusion (n=50)	3 (6.0)	6 (12.0)	14 (28.0)$^+$	15 (30.0)$^+$
SAP <90 mm Hg (n=9)	0 (0.0)	2 (22.2)	3 (33.3)	2 (22.2)
Age >60 yr (n=18)	0 (0.0)	5 (27.8)	8 (44.4)	2 (11.1)

cantly improves outcome in patients with severe head injury, so that it is now a generally accepted therapeutic measure in the pre-hospital management of these patients.[19] However, the results of a number of studies[20–22] indicate that the 'quality' of such a pre-hospital-initiated controlled ventilation has to be improved. In this study the 'quality' of the pre-hospital-initiated controlled ventilation was determined by an arterial blood gas analysis upon hospital admission, which means at the end of the pre-hospital management. Therefore, our results simply reflect the endpoint of a pre-hospital-initiated controlled ventilation.

In only 37.7% of the study population, 'optimal oxygenation' as well as 'adequate' ventilation was achieved after pre-hospital-initiated endotracheal intubation and artificial ventilation upon hospital admission. A detailed review of study findings identified that this is not so much connected with 'oxygenation' but primarily results from 'ventilation' problems. Upon hospital admission 'hypoxaemia' was evident in only three (2.5%) cases and these three patients had severe chest trauma with extensive bilateral pulmonary contusions. In a similar study[20] conducted in 1989 where none of the patients were monitored by pulse oximetry and only one in three of the patients received an $F_{IO_2}=1.0$, the proportion of patients who upon hospital admission had 'hypoxaemia' was 25%.

An ongoing problem is the pre-hospital control of 'ventilation'. We were only able to meet the desired goal of 'normoventilation' in 42.6% of the cases. In the majority of cases (40.9%), the emergency physician unintentionally hyperventilated the lungs, whereas hypoventilation only occurred in 16.4% of cases. Kehrberger and colleagues[20] came to a similar conclusion. Hyperventilation may aggravate cerebral ischaemia[20 22] and, therefore, should be avoided during the pre-hospital phase.[13] This especially applies to patients with 'polytrauma', who in our study were more often unintentionally hyperventilated. These patients additionally are at risk of hypotension, a major determinant in the outcome from severe head injury.[18]

The 'quality' of pre-hospital-initiated ventilation seems to be influenced mainly by the less sophisticated ventilation devices used in the pre-hospital setting in comparison with the in-hospital setting. In the case of manual ventilation using a self-inflating manual resuscitator (i.e. AMBU®-bag) with an additional oxygen supply, it is not possible to measure minute volume; the 'quality' of ventilation depends on the experience and skill of the person 'squeezing' the bag.[23 24] Most of the automatic emergency ventilators allow the ventilatory frequency and minute volume to be set but only some of them (i.e. Oxylog 2000®) measure these preset variables. A number of studies[23 25 26] have shown, that in nearly all commonly used automatic emergency ventilators, the delivered minute volume differs by up to ±20% from the preset minute volume.

Pulse oximetry has proved useful in the detection of hypoxia in the pre-hospital setting.[3] On the other hand there is still no reliable, as well as practical, method for monitoring and controlling 'ventilation' in the pre-hospital setting. Blood gas analysis, the gold standard, seems not to be a practical method for the pre-hospital setting. The use of capnography as a non-invasive as well as continuous monitoring method for controlling 'ventilation' is limited in hypovolaemic patients or patients with severe lung contusion.[3 27]

Without any doubt, endotracheal intubation and controlled ventilation in the field improves the outcome in patients with severe head injury.[4–7] However, our data document that endotracheal intubation and controlled ventilation in the field do not *guarantee* 'optimal' oxygenation and 'adequate' ventilation in patients with severe head injury. In order to optimize the pre-hospital respiratory therapy in such trauma victims, additional respiratory monitoring is necessary.

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Continuous and intermittent cardiac output measurement: pulmonary artery catheter *versus* aortic transpulmonary technique

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Background. Cardiac output (CO) can be measured intermittently by bolus thermodilution methods in the pulmonary artery (COpa) or in the aorta (COart). A continuous thermodilution method (CCO) and a method for continuous estimation using the arterial pulse wave (PCCO) are also available.

Methods. We compared two methods of intermittent CO measurements in patients during liver transplantation: COpa, regarded as the current clinical standard, and an aortic transpulmonary thermodilution technique (COart) performed with the PiCCO system. We also compared CCO and PCCO. Measurements were made in 62 patients at three stages: after the induction of anaesthesia, after caval clamping phase, and at the end of surgery. We used Bland–Altman and correlation analysis.

Results. We found close agreement between the techniques. Mean bias between COart and COpa and PCCO and CCO was 0.15 (2SD of differences between methods=1.74) litre min^{-1} and –0.03 (1.75) litre min^{-1}, respectively. Mean bias between CCO and COpa and PCCO and COpa was 0.02 (1.48) litre min^{-1} and 0.04 (1.69) litre min^{-1}, respectively.

Conclusions. Measurement with the aortic transpulmonary thermodilution technique gives continuous and intermittent values that agree with the pulmonary thermodilution method.

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Cardiac output (CO) and invasive cardiovascular measurements are often used during liver transplantation because instability is common during the procedure.[1] CO is commonly measured by the bolus thermodilution technique (COpa) with a pulmonary artery catheter (PAC). This could miss transient changes in CO during the procedure. A nearly continuous thermodilution method (CCO) uses small quantities of heat and a modified PAC[2–4] with a clinically acceptable accuracy comparable with the intermittent bolus technique (Intellicath for CCO and Sv_{O_2}, Baxter Healthcare Corp., Irvine, CA).[3 5] Recently a method of pulse contour analysis (PiCCO system, Pulsion Medical System, Munich, Germany), which is less invasive than continuous CO monitoring, has been used to give beat-by-beat measurement of continuous CO from the arterial pulse contour analysis (PCCO).[6 7] We compared two methods of intermittent measurement, COart and COpa, and two methods of continuous measurement, PCCO and CCO (Table 1).

Patients and methods

Patients

We obtained approval from the ethics committee and written informed consent from 62 patients (48 male and 14 female) who were about to undergo liver transplantation. We excluded patients with pre-existing pulmonary or cardiac diseases, apart from end-stage liver dysfunction.[8]

Anaesthesia and mechanical ventilation

We applied a lead II/V5 ECG to measure the heart rate and a pulse oximeter and placed a radial artery catheter to measure arterial pressure (AP) (PCM SpaceLabs, Inc., Redmond, WA USA). Anaesthetic management was standardized.

Intermittent positive-pressure ventilation and analysis of inspired gases and end-tidal CO_2 were done with a

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Table 1 Methods used and their abbreviations

Method	**Abbreviation**
Bolus pulmonary artery thermodilution	COpa
Transpulmonary thermodilution	COart
Arterial pulse contour analysis	PCCO
Continuous pulmonary thermodilution	CCO

volumetric anaesthesia ventilator (CATO, Drager Werk HG. Lübeck, Germany). Liver transplantation was done without veno-venous bypass, using the Piggy-back technique. Cathecholamines were used, if needed, to stabilize the circulation during graft reperfusion. Body temperature was controlled to avoid hypothermia, using a warming blanket (Gaymar Meditherm, Orchard Park, NY, USA) and warm intravenous fluids (HOT LINE, SIMS Medical System, Graseby Ltd, UK).

PiCCO monitoring

In all patients, a 4-French gauge thermistor-tipped catheter (Pulsiocath PV2014L, Pulsion Medical System, Munich, Germany) was placed via a 5-French gauge introducer (Adam Spence Europe Ltd, Abbeytown, Boyle, CR, Ireland) through the right femoral artery, and connected to the PiCCO System (version 4.1) for clinical monitoring of AP, PCCO measurements derived from the AP wave, and COart.

Cardiopulmonary monitoring

A modified 7.5-French gauge PAC for Sv_{O_2} and CCO was inserted via an introducer (8.5Fr Baxter Edwards Laboratories, Irvine, CA, USA) into the right internal jugular vein using the Seldinger technique and connected to the Vigilance system (Baxter Edwards Laboratories, Irvine, CA, USA) for COpa and CCO monitoring.

Experimental procedure

COart was calculated from the thermodilution curves using the Stewart–Hamilton principle. The pulse contour device was calibrated after induction of anaesthesia by the mean values of three consecutive COart measurements randomized within the respiratory cycle. These were performed by injection of 15 ml cold saline solution, at a temperature lower than 10°C, via a central venous catheter with subsequent detection by the thermistor embedded into the wall of the arterial catheter. An enhanced version of the Wesseling algorithm, not yet published by the manufacturer, was used to analyse the pulse contour, with a correction factor to reduce the effects of mean AP on arterial impedance as described elsewhere.[6 9 10] PCCO was calculated by multiplying stroke volume by heart rate and presented on the monitor as a moving average of the preceding 12 s. We passed the modified PAC into the pulmonary artery by monitoring the pressure waveform from the distal port of the catheter. Intermittent CO measurements were done by manual injection of 10 ml cold saline solution into the superior vena cava through the atrial port. Three consecutive boluses were injected without regard to the phase of respiratory cycle, over a 2-min period. To avoid variation between operators, the injection was always performed by the same person. The plot of the washout curve was examined for stable baseline temperature, undisturbed rapid upstroke, and exponential decay without signs of early recirculation. If an injection had to be rejected, more injections were made to obtain three measurements after rejecting the lowest and the highest. The setting of the ventilator remained the same during the measurements. Intracardiac and pulmonary AP were monitored continuously to ensure that the catheter was in the correct position. Other intravenous fluids were infused at a constant slow rate during the measurements.

After the induction of anaesthesia and achievement of stable cardiovascular conditions, calibration of the pulse contour analysis system was done before induction of anaesthesia. Intermittent CO measurements were then obtained at specific times during the study period: after induction of anaesthesia (T1), after caval clamping phase (T2) and at the end of surgery (T3). Each set of measurements was made in a steady-state period, that is, at least 15 min after change in dosage of catecholamine or sedatives, infusion rate, or ventilator settings. At each time a single set of haemodynamic measurements was collected when the cardiovascular system was stable. The CO data (bolus and continuous) obtained for calibration and immediately following the calibration are not included in the analysis of PCCO results. At each time, PCCO and CCO were measured immediately before and after intermittent CO measurements and the mean of these PCCO and CCO data pairs recorded. To assess the influence of haemodynamic status on bias, two sets of data pairs were considered according to CO (<8 and >8 litre min^{-1}).

Statistical analysis

All results are expressed as mean (SD) unless indicated otherwise. Statistical analysis used the method described by Bland and Altman.[11] Bias between the methods was calculated as the mean difference between COart and COpa, PCCO and COpa, CCO and COpa, and CCO and PCCO. The upper and the lower limits of agreement were calculated as bias (2SD), and defined the range in which 95% of the differences between the methods were expected to lie. The precision of the bias analysis and limits of agreement was assessed using 95% confidence intervals. This analysis was done for all data obtained at T1, T2 and T3.

Bias between COpa–COart, COpa–CCO, and COpa–PCCO at each stage (T1, T2, T3) was analysed using the paired Student *t* test. CO, mean AP and systemic vascular resistance index (SVRI) were analysed using ANOVA for

Table 2 Patients characteristics and presenting conditions of study population HCV, hepatitis C virus, HBV, hepatitis B virus

Characteristic	**Mean (SD)**	**Range**
Age (yr)	48 (10)	24–66
Body surface area (m^{2})	1.8 (0.2)	1.42–2.15
Male/female	48/14	
Underlying disease		
HCV cirrhosis	22	
HBV cirrhosis	11	
Neoplastic cirrhosis	10	
Alcoholic cirrhosis	8	
HCV + HBV cirrhosis	3	
Cryptogenetic cirrhosis	3	
Hepatic angioma	2	
Other		
Child classification (A/B/C)	15/36/12	
Cold ischaemia time (h)	8.1 (2.1)	5.5–13
Anaesthesia time (h)	10 (1.7)	5.7–14

Table 3 Measurements made after induction of anaesthesia (T1), during the anhepatic phase (T2) and at the end of surgery (T3). Data are mean (SD) AP, arterial pressure, SVRI, systemic vascular resistance index, other abbreviations are given in Table 1 *Significant changes within the study period (analysis of variance); †significantly different from T2 and T1 ($P<0.05$); ‡significantly different from the previous phase ($P\leqslant0.001$)

	T1	**T2**	**T3**
Mean AP (mm Hg)	75 (16)	78 (12)	81 (13)
Range	45–119	61–108	52–116
SVRI (dyne s cm^{5} m^{2})	1310 (307)	1512 (378)‡	1220 (379)‡
Range	1014–2558	1074–2489	1006–2430
COart (litre min^{-1})*	7.6 (2.2)	7.0 (1.9)	8.8 (2.2)†
Range	3.7–13.7	3.2–11.8	4.3–13.3
COpa (litre min^{-1})*	7.5 (2.1)	6.7 (1.8)	8.6 (2.2)†
Range	3.6–13.4	3.3–10.6	4.7–13.5
PCCO (litre min^{-1})*	7.5 (2.3)	6.8 (1.8)	8.7 (2.3)†
Range	4.0–13.0	3.0–11.8	5.0–13.2
CCO (litre min^{-1})*	7.4 (2.3)	6.9 (1.8)	8.7 (2.1)†
Range	3.8–13.8	3.0–11.4	5.0–13.2

Table 4 Mean difference between COart–COpa, CCO–COpa, PCCO–COpa, (bias), and lower and upper limits of agreement (bias±2SD) and coefficient of correlation between the measurements during the procedure Abbreviations as Table 1 *$P<0.0001$

	Bias (litre min^{-1})	**95% limits of agreement**	r^2
COart *vs* COpa	0.15	−1.59 to 1.89	0.86*
PCCO *vs* COpa	0.04	−1.65 to 1.73	0.86*
CCO *vs* COpa	0.02	−1.46 to 1.50	0.88*
PCCO *vs* CCO	−0.03	−1.78 to 1.72	0.85*

repeated measurements and the paired Student *t* test with Bonferroni correction. All statistical analysis was computed by SPSS for Windows (Version 8.0, 1997, SPSS Inc., Chicago, IL). Statistical significance was considered to be at $P<0.05$.

Results

Patient characteristics and the diseases leading to transplant are reported in Table 2. Sixty-two patients were enrolled. PCCO was obtained at each time in all patients. No data were rejected. CO measurements had a range of 3.2–13.7 litre min^{-1} for COart and of 3.3–13.5 litre min^{-1} for COpa. There were 186 pairs of comparative measurements performed between PCCO and CCO. The CO range was 3–13 litre min^{-1} for PCCO and 3–13.8 litre min^{-1} for CCO. CO, mean AP and SVRI measured for the different sample times are reported in Table 3.

The results of the analysis of agreement and the distribution of the observed differences are shown in Table 4 and in Figure 1. Bias was not significantly related to the level of CO but the bias was greater at larger values of CO, without statistical significance (Table 5).

The level of agreement and precision for COart and COpa, PCCO and COpa, CCO and COpa, and CCO and PCCO remained constant throughout the study period. Bias and coefficient of correlation during the predefined analysed steps are reported in Table 6 and Figures 2–4. Correlation between changes in values with each technique in COpa, COart, CCO and PCCO are reported in Table 7.

No adverse effects related to either the PiCCO catheter or the Vigilance Sv_{O_2}/CCO catheter were observed.

Discussion

Thorough cardiovascular measurements are necessary during anaesthesia for liver transplantation. CO is usually measured intermittently but continuous measurement would be preferable. Methods for continuous or semicontinuous measurement with transoesophageal echocardiography or electrical impedance have been investigated during liver transplantation.[12 13]

To our knowledge, this is the first study that compares continuous and intermittent CO measurement obtained with two different devices, the PiCCO System and a modified PAC (Intellicath) in patients undergoing liver transplantation. We confirmed that COart and PCCO measurements agree with COpa, the current clinical standard, and that PCCO agreed well with CCO, showing that measurements of continuous CO can be made successfully by PCCO during transplant surgery. In this study we used the COpa technique as the reference method for all comparisons because it is the current clinical standard.

Previous studies in critically ill patients have reported a small mean difference (bias) and limit of agreement (bias±2SD), considered clinically acceptable, between CCO, based on the pulsed warm thermodilution technique, and COpa measurements.[2 14 15] Our results support the findings of others.[3] Bottiger and colleagues report a bias of 0.24 and a degree of precision of 1.789 litre min^{-1}. In the early phase of transplantation, after inferior vena cava clamping and after graft reperfusion, the accuracy (bias

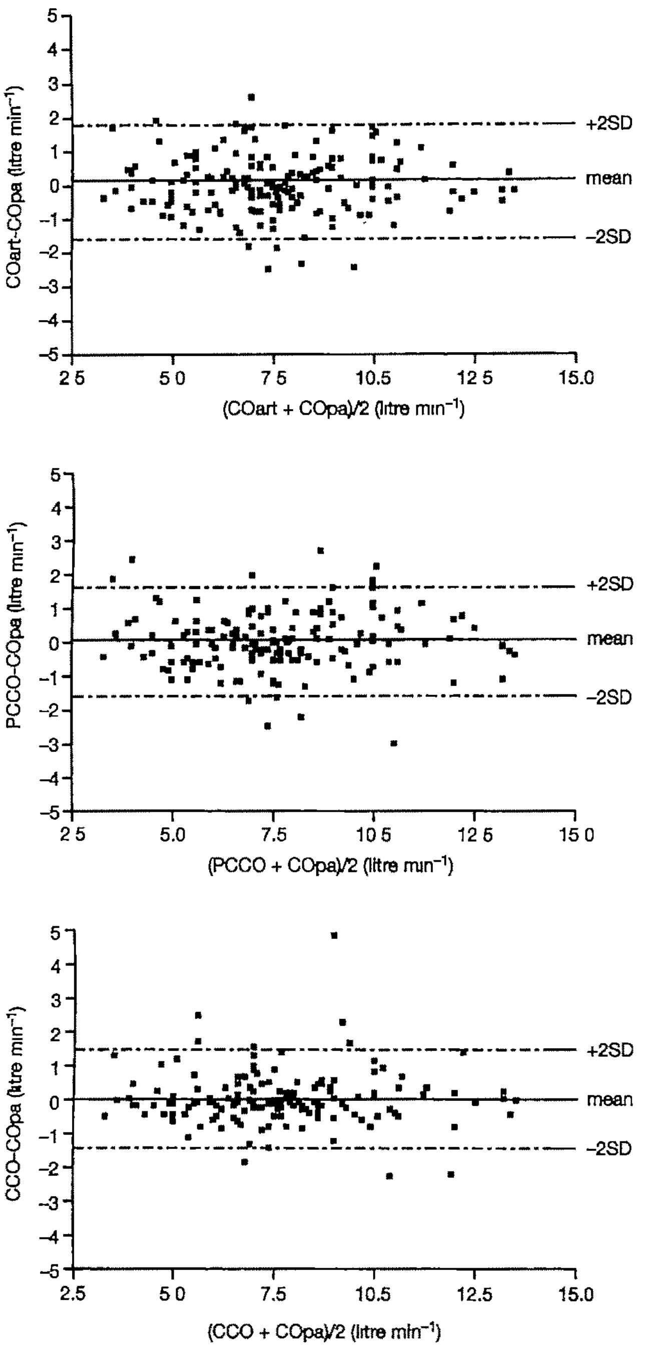

Fig 1 Bland and Altman plots between (from top to bottom) COart and COpa (0.15 [1.74] litre min^{-1}), PCCO and COpa (0.04 [1.69] litre min^{-1}), and CCO and COpa (0.02 [1.48] litre min^{-1}) for all measurements. The unbroken lines show the mean difference and the dotted lines show the 2SD limits of agreement.

0.78 litre min^{-1}) and precision (4.3 litre min^{-1}) were markedly decreased.[3] When we compared CCO and COpa after caval clamping phase we found a bias (2SD) of 0.12 (1.43) litre min^{-1} (Table 6). These differences could be because we do not usually use drug support during inferior vena cava cross-clamping and we carefully avoid hypothermia during liver transplantation so that hypothermia before and immediately after graft reperfusion is prevented.

Table 5 Mean difference between COart–COpa, PCCO–COpa, CCO–COpa (bias), and lower and upper limits of agreement (bias±2SD) at different values of CO. Abbreviations as Table 1

	Cardiac output (litre min^{-1})	**Number of observations**	**Bias (litre min^{-1})**	**95% limits of agreement**
COart *vs* COpa	<8	115	0.01	−1.73 to 1.75
	≥8	71	0.16	−1.62 to 1.47
PCCO *vs* COpa	<8	115	−0.11	−1.63 to 1.41
	≥8	71	0.18	−1.37 to 1.73
CCO *vs* COpa	<8	115	−0.03	−1.29 to 1.23
	≥8	71	0.19	−1.98 to 2.36

Table 6 Mean difference between COart–COpa, PCCO–COpa, CCO–COpa (bias), and lower and upper limits of agreement (bias±2SD) together with coefficient of correlation at sample times. Abbreviations as Table 1. T1, after anaesthesia induction; T2, during anhepatic phase; T3, end of surgery. *$P<0.0001$

	Phase	**Bias (litre min^{-1})**	**95% limits of agreement**	r^2
COart *vs* COpa	T1	0.04	−1.62 to 1.70	0.86*
PCCO *vs* COpa	T1	−0.02	−1.46 to 1.50	0.89*
CCO *vs* COpa	T1	−0.11	−1.84 to 1.63	0.85*
COart *vs* COpa	T2	0.22	−1.72 to 2.16	0.75*
PCCO *vs* COpa	T2	0.09	−1.90 to 2.08	0.72*
CCO *vs* COpa	T2	0.12	−1.31 to 1.55	0.85*
COart *vs* COpa	T3	0.19	−1.35 to 1.73	0.87*
PCCO *vs* COpa	T3	0.07	−1.54 to 1.68	0.87*
CCO *vs* COpa	T3	0.06	−1.32 to 1.44	0.90*

Nowadays the transpulmonary indicator thermodilution technique allows intermittent CO measurement without the need to use a PAC. Animal experiments[16–18] and clinical studies[7 19–21] found a good correlation between pulmonary thermodilution and the transpulmonary thermodilution technique. However, COpa is a measure of right ventricular output whereas COart also measures left ventricular output. Previous studies have found that transpulmonary CO is greater than the corresponding COpa. There may be loss of the cold, and right heart CO may be less than left heart CO because heart rate can be reduced by the cold injection. Approximately 3–4% of the indicator could be lost during passage in the pulmonary circulation, with overestimation of COart.[17 18] Lewis and co-workers[22] described a 9% loss of the injected thermal indicator before femoral detection. Since other studies did not find an indicator loss,[23 24] the transient reduction in heart rate by the cold injection, which has less influence on the COart because of the longer appearance time, is more likely to be responsible for the somewhat lower values of COpa.[25] In the present study COart was higher than COpa, which supports results from other authors.[22–25] Which CO is the true CO cannot be detected by this study. In any case a good agreement between the different techniques was observed. Our results comparing the two intermittent techniques (bias 0.15 [−1.59 to 1.89] litre min^{-1}) are similar to those reported by Gödje and co-workers who studied patients undergoing coronary

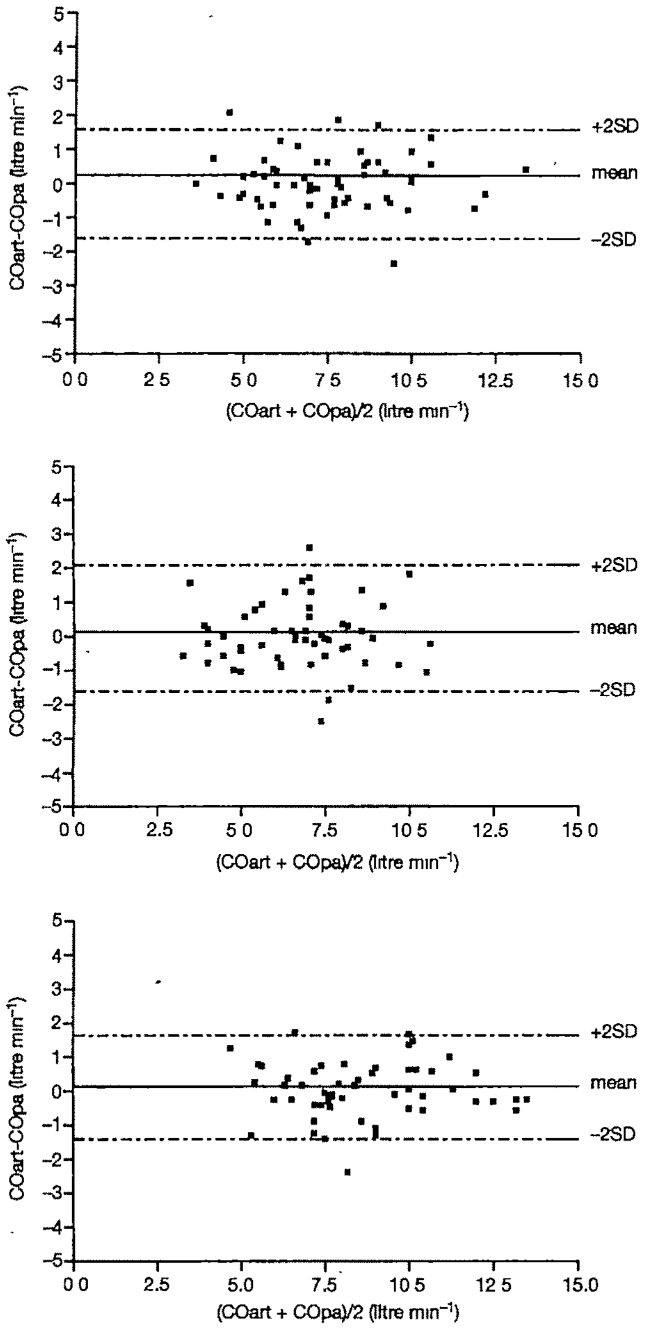

Fig 2 Bland and Altman plots between COart and COpa at specific times· T1 (top, 0.04 [1.66] litre min^{-1}], T2 (middle; 0.22 [1.94] litre min^{-1}), and T3 (bottom; 0 19 [1.54] litre min^{-1}). The unbroken lines show the mean difference and the dotted lines show the 2SD limits of agreement.

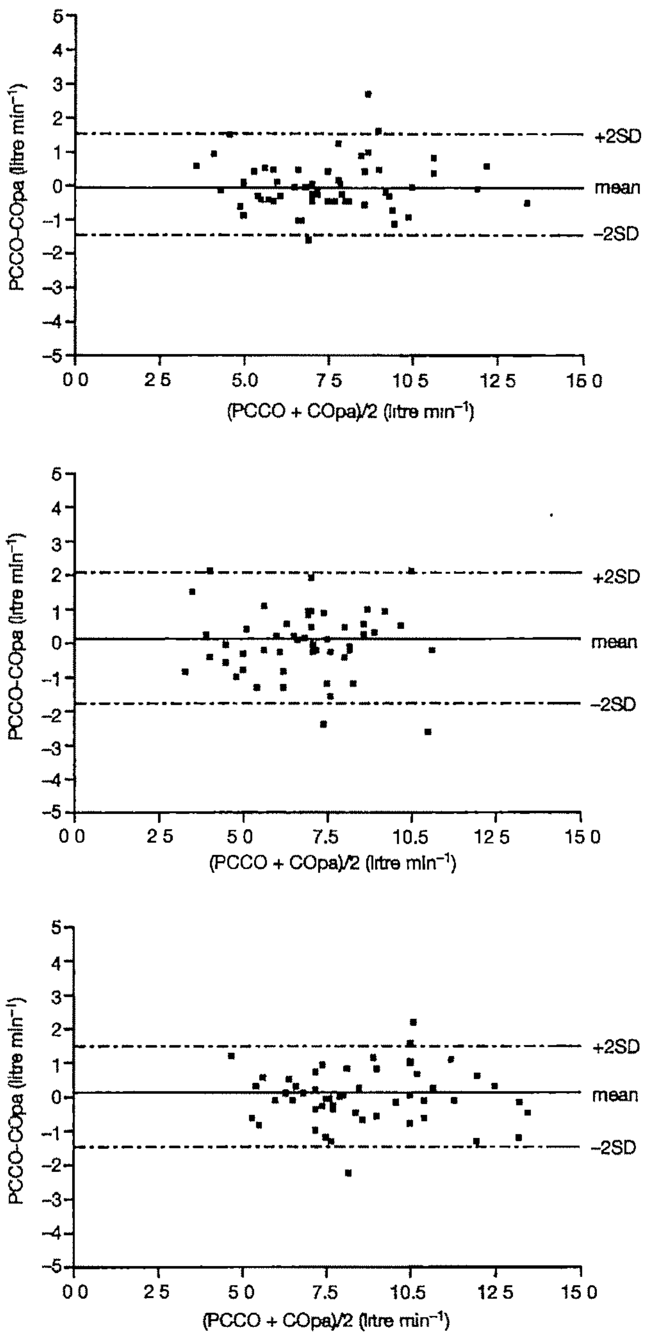

Fig 3 Bland and Altman plots between PCCO and COpa at specific times: T1 (top; −0.02 [1.48] litre min^{-1}), T2 (middle, 0.09 [1.99] litre min^{-1}); and T3 (bottom; 0.07 [1 61] litre min^{-1}). The unbroken lines show the mean difference and the dotted lines show the 2SD limits of agreement.

artery bypass grafting (bias −0.29 [−1.60 to 1.02] litre min^{-1}).[7] In the present study we found a mean difference of 0.04 litre min^{-1} with a level of agreement of 1.69 litre min^{-1} between PCCO and COpa, similar to the results reported by Gödje and colleagues (bias [2SD] 0.07 [1.40] litre min^{-1} and 0.10 [0.42] litre min^{-1}).[7 26] Excellent results (0.003 [1.26] litre min^{-1}) were obtained during cardiac surgery in 12 patients.[27]

Rödig and co-workers showed that changes in vascular tone of approximately 20% did not affect the pulse contour method but large changes in AP may affect PCCO measurements, and re-calibration of the PCCO device may be necessary.[6] The finding that moderate changes in SVR did not necessarily affect the accuracy of PCCO support a study by Irlbeck and colleagues.[28] These authors studied PCCO and COpa in patients in the intensive care

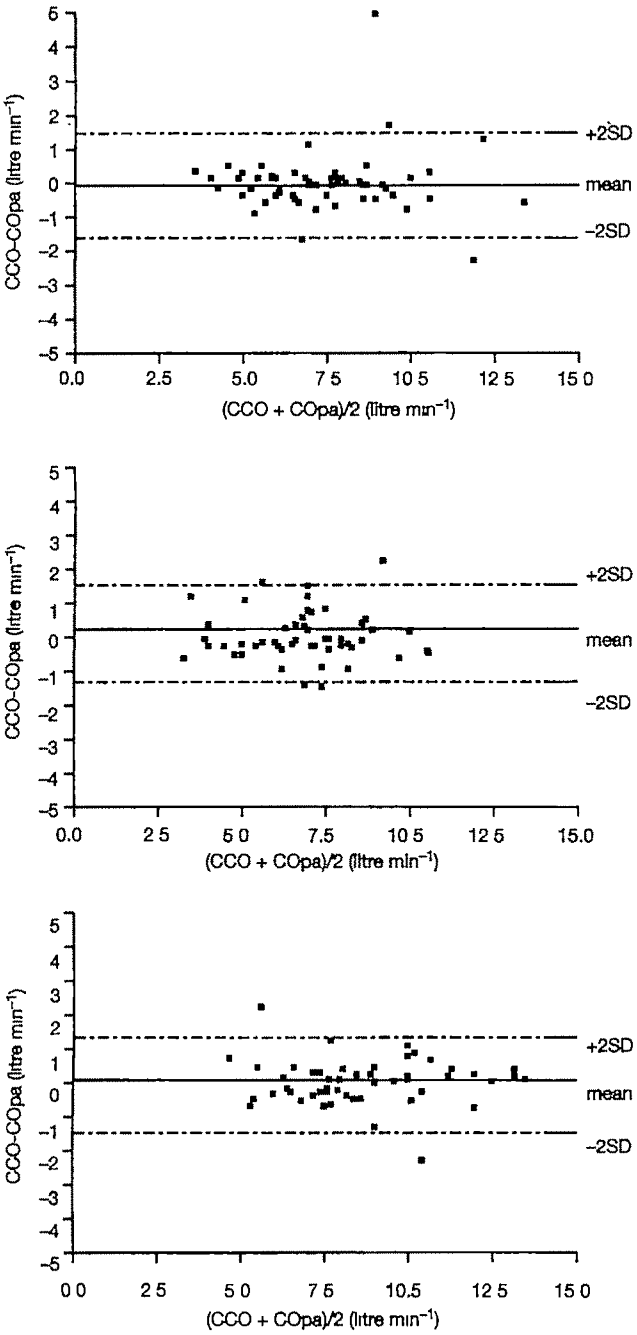

Fig 4 Bland and Altman plots between CCO and COpa at specific times: T1 (top; −0.11 [1.74] litre min^{-1}), T2 (middle; 0.12 [1.43] litre min^{-1}); and T3 (bottom; 0.06 [1.38] litre min^{-1}). The unbroken lines show the mean difference and the dotted lines show the 2SD limits of agreement.

Table 7 Bias between COpa–COart, COpa–PCCO, COpa–CCO changes (Δ), and lower and upper limits of agreement (bias±2SD) together with coefficient of correlation Abbreviations as Table 1 Δ_1=T2–T1; Δ_2=T3–T2 *$P<0.0001$

		Bias (litre min^{-1})	95% limits of agreement	r^2
COpa *vs* COart	Δ_1	−0.10	−2.53 to 2.33	0.64*
COpa *vs* PCCO	Δ_1	0.04	−2.50 to 2.58	0.64*
COpa *vs* CCO	Δ_1	−0.12	−2.23 to 1.99	0.75*
COpa *vs* COart	Δ_2	−0.04	−1.91 to 1.83	0.76*
COpa *vs* PCCO	Δ_2	−0.01	−2.02 to 2.00	0.74*
COpa *vs* CCO	Δ_2	0.02	−1.59 to 1.63	0.82*

unit and concluded that PCCO is valid for clinical purposes only if the initial calibration is repeated every 4 h.[28] We found no evidence that PCCO was not accurate even with substantial changes in SVR. The changes in vascular tone in our patients were probably less and had no effect on the pulse contour method. The site of pulse contour detection may be important. The pressure in peripheral arteries (such as the radial artery) may be influenced by the reflection of pulse waves and greater transit time, which can interfere with the calculation of PCCO. In this study, PCCO was always measured with a catheter in the abdominal aorta, passed from the femoral artery. Problems with arterial catheters in the radial or brachial artery during periods of low CO were avoided. We did not observe a decrease in PCCO and/or CCO after injection of cold saline at any time during the procedures, despite giving large volumes of fluids that could affect the reliability of the continuous thermodilution CO measurements.[3] At greater values of CO (>8 litre min^{-1}) the limits of agreement between PCCO–COpa and between CCO–COpa were −1.37 to 1.73 litre min^{-1} and −1.98 to 2.36 litre min^{-1}, respectively (Table 5).[29] Clinically the response to haemodynamic changes is more accurate with PCCO based on AP waveform than CCO because the latter method requires measurement over 3 min, being a semicontinuous method.

The risks of PAC have been recently discussed.[30] The transpulmonary thermodilution method performed with the PiCCO or COLD system requires a central venous cannula to inject cold saline, and a femoral arterial cannula, and avoids the use of a PAC.[9 21 22 27] Given the closer correlation between the methods, the pulse contour method for determination of CO can be calibrated and made using COart, which would avoid unnecessary insertion of a PAC.[7 26 27] A central venous cannula is necessary in most surgical patients anyway, and femoral artery catheterization, which allows continuous haemodynamic monitoring and blood sampling, is safe in critically ill patients.[31]

In conclusion, PAC insertion seems to be justified only when continuous measurement of Sv_{O_2} is needed, or in patients with pulmonary hypertension. The PiCCO system is very useful in high-risk patients if less invasive monitoring is required.

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Cerebrovascular carbon dioxide reactivity in children anaesthetized with sevoflurane

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Background. To determine the effects of sevoflurane on cerebrovascular carbon dioxide reactivity (CCO_2R), middle cerebral artery blood flow velocity (CBFV) was measured at different levels of PE'_{CO_2} by transcranial Doppler sonography in 16 ASA I or II children, aged 18 months to 7 yr undergoing elective urological surgery.

Methods. Anaesthesia comprised 1.0 MAC sevoflurane and air in 30% oxygen delivered through an Ayre's T piece by intermittent positive-pressure ventilation, and a caudal epidural block with 0.25% bupivacaine 1.0 ml kg^{-1} without epinephrine. PE'_{CO_2} was randomly adjusted to 25, 35, 45 and 55 mm Hg (3.3, 4.6, 5.9 and 7.2 kPa) with an exogenous source of CO_2, while maintaining ventilation variables constant.

Results. CBFV increased as PE'_{CO_2} increased from 25 to 35, and to 45 mm Hg ($P<0.001$), but did not increase significantly with an increase in PE'_{CO_2} from 45 to 55 mm Hg. Mean heart rate and arterial pressure remained constant.

Conclusion. CCO_2R is preserved in healthy children anaesthetized with 1.0 MAC sevoflurane.

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The technique of controlled hyperventilation, with the consequent reduction in Pa_{CO_2}, is used during general anaesthesia to lower raised intracranial pressure caused by intracranial disease. It acts through the mechanism of cerebrovascular carbon dioxide reactivity (CCO_2R) to reduce both cerebral blood flow and cerebral blood volume. It has been reported that cerebrovascular reactivity is preserved during isoflurane anaesthesia in children.[1] It is also preserved during sevoflurane anaesthesia in adults,[2–5] although CCO_2R during sevoflurane anaesthesia was less than that observed during isoflurane anaesthesia in the same group.[5] The aim of this study was to determine the effect of varying concentrations of expired CO_2 on cerebral blood flow velocity (CBFV) in children during sevoflurane anaesthesia.

Patients and methods

Following Research Ethics Board approval and written informed parental consent, 16 ASA physical status I or II, unpremedicated children aged 18 months to 7 yr, undergoing elective urological surgery were studied. Children with neurological, pulmonary or congenital heart disease, a history of premature birth or a contraindication to regional anaesthesia were excluded.

Anaesthesia was induced with sevoflurane and air in oxygen. Rocuronium 0.6 mg kg^{-1} was administered to facilitate tracheal intubation and the size of the uncuffed tracheal tube was chosen to allow only a minimal leak at an inspiratory pressure of 20 cm H_2O. Anaesthesia was maintained with 1.0 MAC (age adjusted) sevoflurane[6] and air in 30% oxygen delivered through an Ayre's T piece by intermittent positive-pressure ventilation with zero end-expiratory pressure (Kion, Siemens, Sweden). Repeat doses of rocuronium were administered as required to maintain neuromuscular blockade. All patients received a caudal epidural block with 0.25% bupivacaine 1.0 ml kg^{-1} without epinephrine. Body temperature was monitored rectally and maintained constant with a conductive water mattress and

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convective air warmer under the surgical drapes. The patients were kept supine and horizontal throughout the study period. Following stabilization of maintenance anaesthesia, ventilation was adjusted to achieve a PE'_{CO_2} of 25 mm Hg (3.3 kPa). Thereafter, fresh gas flow and ventilation variables were maintained constant. The $PE'_{CO_2}$was randomly adjusted to 25, 35, 45 and 55 mm Hg (3.3, 4.6, 5.9 and 7.2 kPa) by the addition of CO_2 to the Ayre's T piece from an exogenous source. The first and subsequent levels of PE'_{CO_2}were determined randomly until the last one was reached. The randomization was undertaken using computer-generated random number tables. Measurements were started after a 3 min stabilization period following changes in PE'_{CO_2}.

CBFV was measured by transcranial Doppler (TCD) sonography (Neuroguard, Medasonics, CA). The M1 segment of the middle cerebral artery was insonated through the temporal window with a range-gated 2 MHz Doppler probe, which was fixed to the subject's head using a special device to maintain a constant angle of insonation throughout the study period.[7] Additional technical specification of the TCD probe and details of Doppler analysis have been described.[1] Three measurements were made, at 1-min intervals, at each PE'_{CO_2}. The TCD data were recorded on a computer and subsequently analysed by one investigator who was unaware of the sequence of changes in PE'_{CO_2}. Mean CBFV was calculated as the time-averaged area under the curve of 10 consecutive Doppler tracings. Non-invasive arterial pressure, heart rate, end-tidal sevoflurane concentration, airway pressure, ventilatory frequency, Sa_{O_2} and rectal temperature were recorded at each level of PE'_{CO_2} (SC 9000XL; Siemens, Sweden). The CO_2 was sampled from the tracheal tube using a 19G catheter (Intracath; Becton Dickinson, CA) and the CO_2 analyser (Capnomac Ultima, Datex, USA) was calibrated with a reference gas mixture before each study patient.

Statistical analysis

All data with parametric values are expressed as mean (SD). The number of patients needed to demonstrate a direct effect on CBFV during changes in PE'_{CO_2} was calculated with the assumption that a 20% change would be clinically relevant. Based on previous data[8] demonstrating a CBFV of 78 (SD 21) cm s^{-1} with 1.0 MAC sevoflurane at 40 mm Hg (5.3 kPa) PE'_{CO_2} in a comparable group of children, and a statistical power of 0.8, an $\alpha_2=0.05$ and $\beta=0.2$, a total of seven patients was suggested. Sixteen patients were studied to account for methodological difficulties that could have led to exclusion from the study. The relationship between PE'_{CO_2} and CBFV was obtained by non-linear regression analysis and the correlation coefficient (r) was calculated. Parametric data were analysed by repeated-measures ANOVA and the Student–Newman–Keuls test for multiple comparisons where appropriate. A value of $P<0.05$ was accepted as significant. The degree of relative dispersion was measured using the coefficient of variation for the CBFV data, which helps to determine the extent of the measurement effect on the results.

Results

The mean age of the 16 children was 4 (SD 1.6) (range 1.5–7) yr and the mean weight was 16.8 (SD 4.6) (range 8.4–26) kg. Heart rate and mean arterial pressure remained constant throughout the study period (Table 1). The caudal block was successful in all cases. The TCD measurements were completed in all children, at all levels of PE'_{CO_2}, and there were no complications observed with the use of TCD sonography in this study. The CBFV increased markedly as PE'_{CO_2} was changed from 25 to 35 mm Hg (3.3 to 4.6 kPa) ($P<0.001$) and from 35 to 45 mm Hg (4.6 to 5.9 kPa) ($P<0.001$). However, CBFV did not increase significantly when the PE'_{CO_2} was raised from 45 to 55 mm Hg (5.9 to 7.2 kPa) (Table 1). The correlation coefficient (r) between CBFV and $PE'_{CO_2}$was 0.89 (Fig. 1). The CCO_2R expressed as the percentage change in mean CBFV for a 1 mm Hg change in PE'_{CO_2} was 8.6% as PE'_{CO_2} increased from 25 to 35 mm Hg, and 5.1% from 35 to 45 mm Hg. It was only 0.8% as PE'_{CO_2} increased from 45 to 55 mm Hg (Table 2). The degree of relative dispersion measured using the coefficient of variation for the CBFV data was 8.9%.

Discussion

The results of this study demonstrate that CCO_2R is preserved in healthy children anaesthetized with 1.0 MAC sevoflurane. Similar findings have been reported in adults anaesthetized with sevoflurane.[2-5] CO_2 exerts a rapid and considerable influence on the cerebral circulation by dilating the cerebral arterioles and increasing cerebral blood flow. It has been postulated that this effect occurs

Table 1 Variations in cerebral blood flow velocity (CBFV) and haemodynamic variables with increasing PE'_{CO_2} in children anaesthetized with 1.0 MAC sevoflurane. Results are expressed as mean (SD) $^*P<0.001$ with 25 mm Hg, $^\dagger P<0.001$ with 35 mm Hg.

PE'_{CO_2}(mm Hg) **(kPa)**	**25** **3.3**	**35** **4.6**	**45** **5.9**	**55** **7.2**
CBFV (cm s^{-1})	35 (7)	64 (16)*	94 (18)*†	102 (20)*†
Mean arterial pressure (mm Hg)	62 (10)	65 (12)	65 (10)	66 (11)
Heart rate (beats min^{-1})	111 (10)	109 (9)	110 (9)	108 (9)

as a result of rapid diffusion of CO_2 from the arterial blood into arteriolar smooth muscle causing a change in extracellular pH.[9] The observed CCO_2R of 8.6% with sevoflurane in the present study is considerably greater than the 2.6% with 1.0 MAC isoflurane and 1.4% with 1.0 MAC halothane reported by Leon and Bissonnette in a comparable group of children using a similar protocol.[1] It is also greater than the 2.1% reported by Nishiyama and colleagues with 0.7 MAC sevoflurane in adults.[5] Hence during sevoflurane anaesthesia in children, small changes in $P\text{E}'_{CO_2}$ could have a clinically significant effect on cerebral blood flow and intracranial pressure. Furthermore, Nishiyama and colleagues reported that CCO_2R was greater for isoflurane than for sevoflurane in adults, but comparison of the data of the present study with that reported by Leon and Bissonnette suggests that the opposite may be true in children.[1 5]

A plateau in CCO_2R between a $P\text{E}'_{CO_2}$ of 45 and 55 mm Hg was observed in this study, which was also observed by Leon and Bissonnette with isoflurane in children, but has not been reported with any volatile agent in adults.[1] In children, unlike adults, cerebral vasodilatation seems maximal with 1.0 MAC sevoflurane above 45 mm Hg $P\text{E}'_{CO_2}$. Pilato and colleagues have also demonstrated this effect in a comparable group of children undergoing intravenous anaesthesia without a volatile agent.[10] This may suggest that the observed effect is a characteristic of the cerebral vasculature in this age group and not an effect of the volatile agent. It has been demonstrated that acute hypercapnia can reduce the capacity for cerebral autoregulation, presumably with a loss of cerebrovascular vasodilatation in response to changes in perfusion pressure.[11] This effect may therefore be occurring at or above the upper range of normal $P\text{E}'_{CO_2}$ in children anaesthetized with 1.0 MAC sevoflurane.

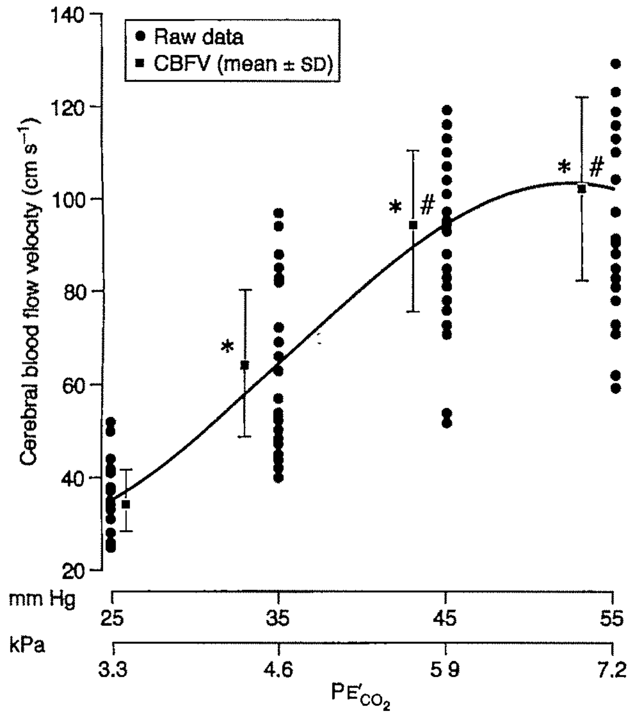

Fig 1 Relationship between cerebral blood flow velocity (circles, raw data; squares, mean values) and $P\text{E}'_{CO_2}$. Non-linear regression analysis provided the best-fit line shown. The correlation coefficient (r) is 0.89. $^*P<0.001$ with 25 mm Hg, $^\#P<0.001$ with 35 mm Hg.

The stability of the heart rate and mean arterial pressure throughout the study period suggests that the observed changes in CBFV were not a result of cardiovascular alteration nor were they likely to have been caused by surgical stimulation, which seems to have been successfully obtunded by the caudal epidural block. Other determinants of CBFV were also controlled.[1] Body temperature and depth of anaesthesia were maintained constant. Intrathoracic pressure was maintained constant by keeping the fresh gas flow rate and ventilation variables at the settings required to achieve the initial $P\text{E}'_{CO_2}$ of 25 mm Hg throughout the study period. The $P\text{E}'_{CO_2}$ was changed by addition of CO_2 to the T piece from an exogenous source, preventing any alteration in intrathoracic pressure and cerebral venous return.

Normal CBFV changes with age, increasing rapidly from birth to approximately 18 months, followed by a relatively minimal increase up to a peak at 7 yr and thereafter declining with increasing age.[12] Thus CBFV in our study population, aged 18 months to 7 yr, should be relatively unaffected by age. The Doppler probe was fixed to the subject's head, using a custom-designed frame, to maintain a constant angle of insonation (i.e. the angle at which the Doppler beam impacts on the artery) throughout the study period and hence avoid intrapatient errors in the calculation of CBFV.[13] Interpatient variability in the calculation of CBFV can result from different probe positions causing changes in the angle of insonation, which can range from 0 to 30 degrees for the middle cerebral artery.[14] These variations could result in a maximum measurement error of 15%.[14] The calculated coefficient of variation for both intra- and interpatient measurements demonstrated a relative dispersion within acceptable experimental limits. It has been shown that cerebral blood flow responds rapidly to

Table 2 Variations in cerebrovascular CO_2 reactivity (CCO_2R) expressed as the percentage change in mean CBFV for a 1 mm Hg change in $P\text{E}'_{CO_2}$ with increasing $P\text{E}'_{CO_2}$ in children anaesthetized with 1 0 MAC sevoflurane. Results are expressed as mean (SD).

$\Delta P\text{E}'_{CO_2}$(mm Hg) **(kPa)**	**25–35** **3.3–4.6**	**35–45** **4.6–5.9**	**45–55** **5.9–7.2**
CCO_2R (% mm Hg)	8.6 (2.9)	5.1 (3 2)	0 8 (0 5)

changes in Pa_{CO_2} and reaches a plateau within 2 min.[9] Three min was allowed after each change in PE'_{CO_2} to achieve steady-state conditions within the brain. There was no variability between the first and third measurements at each level of PE'_{CO_2}, which allows us to assume that the steady-state conditions for CO_2 were present within the basal arteries of the brain during the measurement periods. The PE'_{CO_2} was sampled from the connector of the tracheal tube to prevent any mixing effect from the fresh gas flow.[15] Furthermore, it has been shown that PE'_{CO_2} closely approximates to Pa_{CO_2} in healthy children.[16,17] Young and colleagues reported that the cerebral blood flow response to changes in CO_2 tension in adults can be reliably estimated from measurement of PE'_{CO_2}.[18] Having accounted for all the confounding factors that could affect the CBFV and the possible measurement errors, one can conclude that the observed changes in CBFV are attributable to changes in PE'_{CO_2}.

TCD sonography was used to measure the effect of changing PE'_{CO_2} on CBFV. It is a simple non-invasive and reproducible method of measuring CBFV. Relative changes in CBFV have been shown to correlate well with changes in cerebral blood flow measured by intravenous xenon^{133} clearance (r=0.84) and radioactive microspheres (r=0.94).[19,20] In order for this to be true, the cross-sectional area of the M1 segment of the middle cerebral artery must not alter significantly with changes in arterial pressure, Pa_{CO_2} or the use of anaesthetic agents. This has been verified by direct measurement during craniotomy, and using both angiography and Doppler signal power analysis.[21–23] Furthermore, Gillard *et al.* have demonstrated the reliability of TCD to insonate the M1 segment of the middle cerebral artery through the temporal window in the paediatric population.[24] TCD sonography is now widely used as a surrogate measure of cerebral blood flow.[25]

Sevoflurane appears to demonstrate the properties of a suitable anaesthetic agent for adult neurosurgical procedures. It causes less intrinsic cerebral vasodilatation and preserves dynamic cerebral autoregulation in response to changes in mean arterial pressure.[3,4,26–28] It does not seem to cause an epileptiform EEG or an increase in intracranial pressure during neurosurgery.[29,30] The present study shows that, with respect to CCO_2R, sevoflurane could be a suitable agent for paediatric neurosurgical procedures. We have previously shown in children that CBFV is not affected by changes in sevoflurane concentration from 0.5 to 1.5 MAC.[8] We have also reported that the effect on CBFV of adding nitrous oxide to sevoflurane is similar to adding it to isoflurane.[31] Taking account of all of these findings, we can say that sevoflurane demonstrates some of the ideal properties of an anaesthetic agent for paediatric neurosurgical procedures. However, a direct clinical comparison of sevoflurane with other anaesthetic agents is necessary to decide which is the ideal agent for this indication.

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Recovery of memory after general anaesthesia: clinical findings and somatosensory evoked responses

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Background. Mid-latency somatosensory evoked responses are used to monitor the integrity of the sensory pathways intra-operatively. They can quantify the effects of anaesthetics on the central nervous system. Mid-latency auditory evoked responses have been related to cognition during anaesthesia, but there are no detailed studies using median nerve somatosensory evoked responses (MnSSER).

Methods. We studied 49 patients during recovery from general anaesthesia (isoflurane/nitrous oxide or propofol) to assess implicit and explicit memory function in relation to mid-latency MnSSER. The MnSSER recordings were made before anaesthesia, during steady-state anaesthesia, and at the end of the recovery period. The patients were interviewed 24 h later about their memory for the immediate wake up phase. Statistical analysis was by multivariate analysis of variance.

Results. Out of 49 patients, 23 recalled the recovery period, 11 had implicit memory for an object shown to them during the recovery period, and 15 did not have any memory for the recovery period. At RECOVERY the patients with recall had significantly shorter MnSSER latencies N45 and P50 and inter-wave conduction times LatN35 – LatP45 than patients without memory ($P<0.05$).

Conclusions. We conclude that MnSSER components warrant further investigation for studying the effects of anaesthetic drugs on cognitive function.

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Although large clinical surveys report explicit awareness in less than 0.2% of patients during anaesthesia for general surgery, this adverse-event is a great concern, because the patients may be permanently affected by the experience.[1] Recall of intra-operative events will presumably occur if information processing is not adequately blocked by anaesthetics. During anaesthesia there is no clinical sign indicating the likelihood of persistent memory, so indirect signs are used to judge the state of the patient. Measurements from the spontaneous and the evoked electroencephalogram (EEG) have been introduced to assess cerebral function during general anaesthesia. The bispectral index, a computer-derived parameter of the spontaneous EEG, and the auditory evoked response (AER), may allow assessment of persistent memory during anaesthesia,[2] but there is no standard means to assess memory during anaesthesia.

Median nerve somatosensory evoked responses (MnSSER) have not been studied in relation to memory during anaesthesia. However, MnSSER can be part of standard monitoring for neurosurgical, vascular, or orthopedic procedures, when nervous structures are at risk during the operation. Therefore, it is interesting to find out if they provide further information about cerebral signal processing other than information about the integrity of the sensory pathway. MnSSER can indicate cortical arousal during surgical stimulation.[3] We do not know if they indicate the analgesic component during anaesthesia, whereas the AER may reflect the hypnotic component.[4 5] We have shown, that MnSSER changes in relation to clinical awakening during

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recovery from general anaesthesia.[6] Theoretically, MnSSER could be used for monitoring during anaesthesia, if AER recording was not practical, for example as a result of hearing problems in patients.

We set out to describe memory and mid-latency MnSSER during recovery from general anaesthesia. The recovery period was chosen because the incidence of persistent memory during surgical anaesthesia is supposed to be low. The present investigation describes memory performance, while recovery of MnSSER with decreasing anaesthetic dose has been published previously.[6]

Patients and methods

Patients

With approval from the local ethics committee and written informed consent, we prospectively studied 49 female patients (mean 41 (SD 12) [range 18–67] yr, 1.67 (0.08) m, 67.9 (14) kg, ASA I–II), about to have elective gynaecological operations of about 1 h. We excluded patients with neurological diseases. No patients were taking centrally acting drugs.

Anaesthesia

All patients were given midazolam 7.5 mg orally as a premedication 45 min before anaesthesia. According to their date of birth, patients were allocated to two different anaesthetic treatments. In one group, anaesthesia (n=20) was induced with propofol 2 mg kg^{-1}, sufentanil 0.5 μg kg^{-1}, and vecuronium 0.1 mg kg^{-1}. After tracheal intubation, anaesthesia was maintained with propofol 8 mg kg^{-1} h^{-1}. Supplementary doses of sufentanil 0.25 μg kg^{-1} were given as necessary. The patients in the other group (n=29) received etomidate 0.3 mg kg^{-1}, fentanyl 1.5 μg kg^{-1}, and vecuronium 0.1 mg kg^{-1} for induction of anaesthesia. After trachea intubation, anaesthesia was with isoflurane 0.6% (end-tidal) in nitrous oxide/30% oxygen supplemented with doses of fentanyl 0.5 μg kg^{-1}. At the end of surgery, when median evoked responses had been recorded during anaesthesia, the administration of the anaesthetics was stopped and 100% oxygen was given (fresh gas flow 3 litre min^{-1}). When breathing was adequate, the tracheal tube was removed.

Memory assessment

When the patients regained consciousness and opened their eyes spontaneously after anaesthesia, they were asked to name precisely an object that they were shown. This was a red booklet, which was opened and closed in front of them. They were asked to keep this booklet in mind.

The next day, the patients were asked about their memory after immediate waking using a structured interview. They were asked a broad variety of questions, and the relevant questions are listed in Table 1. If they did not recall anything spontaneously, five different objects including the red booklet were shown to them. They were asked to point at one of the objects.

Table 1 Structured interview 24 h after anaesthesia

What was the first you remembered after waking up from anaesthesia?
Do you remember anything to be shown to you during the wakeup period?
Do you remember whether the MnSSER recording was performed?
Were you asked to keep anything in mind during recovery from anaesthesia?

The patients were classified into three groups according to their memory for the immediate wake-up period, as evaluated by the structured interview on the first post-operative day. These were patients who recalled either the shown object or the MnSSER monitoring spontaneously (EXPLICIT); patients who chose the red booklet from the four other objects, but did not recollect anything spontaneously from the recovery period (IMPLICIT); and the patients who did not have any memory for the immediate wake-up phase (NO-MEM).

MnSSER recording

The day before surgery the patients were accustomed to MnSSER recording to obtain awake baseline values. The MnSSER recording was performed in a standardized way with an Evomatic 4000® system (Dantec, Copenhagen, Denmark). In preference the right median nerve was stimulated, but if the planned operation made that difficult, the median nerve was used. The individual sensory and motor threshold was defined. The stimulus intensity was increased to the individual level of tolerance and kept constant throughout the whole study. Two replicate baseline recordings were performed. The stimulus frequency was 3 Hz, with a monophasic rectangular pulse of 0.2 ms. The MnSSER waveforms were recorded simultaneously on three amplifier channels using sterile platinum needle electrodes placed over the ipsilateral brachial plexus (Erb's point), the spinous process of the sixth cervical vertebra and the contralateral cortical hand area at the scalp (C3′ or C4′). A frontal reference (Fpz) was used. Electrode impedances were kept below 10 kΩ. For the baseline data a post-stimulus period of 90 ms was analysed, during anaesthesia and recovery a period of 180 ms. For each response, 200 stimuli were averaged and stored on disk for later analysis. The Evomatic device includes an automatic artefact rejection mode, and the evoked responses at Erb's point and at the spinous proces level served as a control for artefacts, analysed by visual inspection. The latencies and the peak-to-peak amplitudes were obtained using a software package (EvoPC®, Müller, Hamburg, Germany). The following peak latencies were obtained: N10 at Erb, N13 at C6 and three negative components (N20, N35, N50) and two positive peaks in between (P25, P45) at the scalp.

Two replicate MnSSER recordings were performed the day before surgery (AWAKE), during anaesthesia after surgery had finished (ANAESTHESIA) and when the patients opened their eyes spontaneously and named the shown object correctly after anaesthesia (RECOVERY).

Clinical measurements

We recorded heart rate (beats $\min^{-1}$), mean arterial pressure (mm Hg), percutaneous oxygen saturation (%), and arm and body temperature, at the time the MnSSER recording was made. During and after anaesthesia the end-tidal carbon dioxide concentration was measured (either from the tracheal tube, or from a face mask, which was applied firmly and the patient was asked to take some deep breaths).

Statistical analysis

The statistical analysis was done using SPSS version 9.0 (Statistical Package for Social Sciences). The patient details of the different groups were compared a posteriori with Scheffé's test. The mean and the standard deviations (SD) of the various cortical peak latencies and amplitudes were calculated, and the inter-wave conduction times of the latency components were calculated: LatN20 – LatC6 (CCT=central conduction time), LatP25 – LatN20, LatN35 – LatP25, LatP45 – LatN35, and LatN50 – LatP45. The distribution of the data was tested by the Kolmogorov–Smirnov test. The correlation coefficients were separately defined for the five latencies, the five inter-peak latencies, and the four amplitudes.

Inter-group comparisons for the MnSSER latencies (five components), the latency differences (five components), and the amplitudes (four components) for the three memory groups were assessed by multivariate analysis of variance for repeated measurements (MANOVA, Hotelling's T-square) including AWAKE and RECOVERY values. Multivariate comparisons were performed for the five latency components, the five inter-peak latency components and the four cortical amplitudes separately at AWAKE, ANAESTH, and RECOVERY values. For each MnSSER component, univariate analysis of variance compared the data at AWAKE and RECOVERY. The sensitivity and specificity were calculated for the significant MnSSER components to define cuff-off values for memory perfomance. $P<0.05$ was adopted for level of significance for all statistical tests.

Results

Explicit and implicit memory

At interview 24 h after anaesthesia, 15 patients had no memory for the immediate wake-up period. Eleven patients had implicit memory for the booklet, and 23 had explicit memory. Of these 23, 13 remembered the booklet spontaneously and 12 recalled at least one MnSSER recording being performed. However, another three patients spontaneously described precisely being asked to take a deep breath from the mask, which was tightly pressed on their face. They were included in the group EXPLICIT, because this procedure was done during the immediate recovery period to measure respiratory values. Only five patients remembered both the MnSSER recording and the booklet spontaneously. However, another four had implicit memory for the shown booklet, and remembered the MnSSER recording. One patient, who recalled taking a deep breath, had implicit memory for the booklet. However, two patients of the group EXPLICIT recalled extubation.

MnSSER components

Satisfactory MnSSER traces were obtained at the different measurements from all patients. Figure 1 gives examples of the MnSSER recordings of three patients, one without any memory, one with implicit memory, and one with explicit memory. There was no difference for any of the MnSSER components at AWAKE among the three memory groups. Multivariate analysis showed an overall significant difference between the three groups, comparing the MnSSER data at AWAKE and RECOVERY for the latency components and for the inter-wave conduction times (Table 2A–C). The cortical amplitudes did not differ significantly. The MnSSER data at ANAESTH were not included in the multivariate test, because N35 was completely suppressed in seven patients, P45 in 16 and N50 in 22 patients, thus reducing *n* for statistical testing markedly. However, univariate comparison at ANAESTH revealed significantly shorter latencies N20 and P25, comparing patients of group EXPLICIT with patients of group NO-MEM ($P<0.05$). The components ≥35 ms were completely reduced in more patients of group NO-MEM and IMPLICIT than in patients of group EXPLICIT (Fig. 2).

At RECOVERY Hotellings' T-square showed significant main effects for the latency ($P<0.01$) and the inter-wave conduction times ($P<0.001$) among the three memory groups. The amplitudes did not differ at RECOVERY. ANOVA showed significant differences for latencies P45 ($P<0.05$) and N50 ($P<0.01$), as well as for the conduction times LatP45 – LatN35 ($P<0.01$) and LatN50 – LatP45 ($P<0.05$). Post hoc comparison revealed significant shorter latencies P45 ($P<0.05$) and N50 ($P<0.05$) and inter-peak latency LatN35 – LatP45 ($P<0.05$) for the patients of the group EXPLICIT compared with the patients of the group NO-MEM. Using a cut-off value of 14 ms for the latency P45 yielded a sensitivity of 87.0% and a specificity of 61.5% to predict patients with no memory (for N50, a cut-off value of 21 ms, sensitivity 69.6%, specificity 76.9%).

The MnSSER data of the three memory groups did not differ in relation to the used anaesthetic. However, the changes of latencies P45 and N50 and inter-wave conduction times LatN35 – LatP45 and LatP45 – LatN50 were significantly correlated with the duration of anaesthesia (P=0.016 for latencies, P=0.007 for inter-wave conduction times).

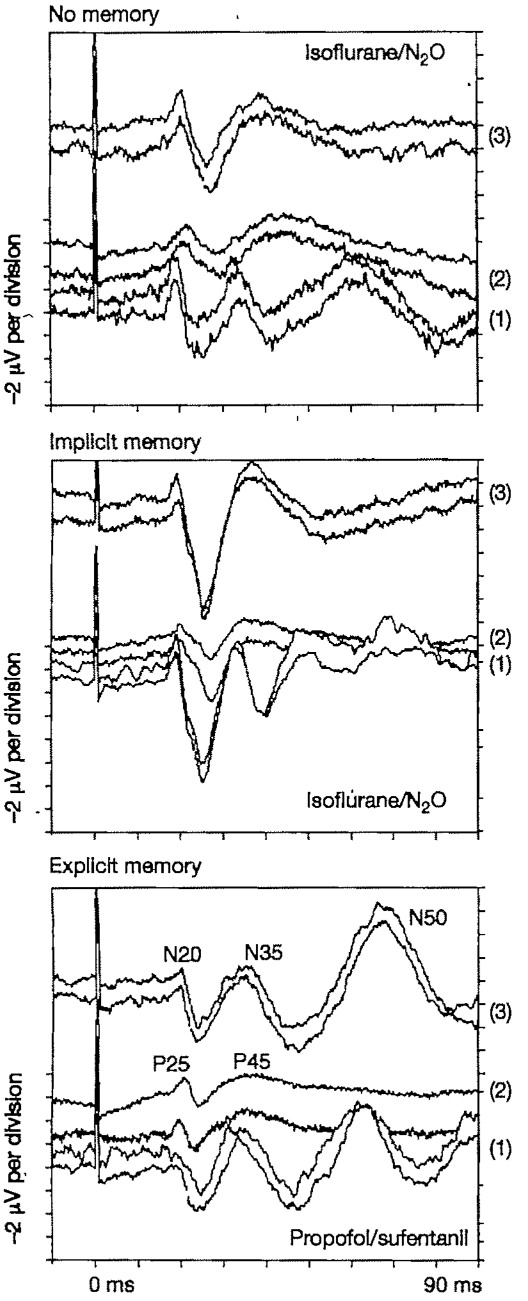

Fig 1 MnSSER recordings after electrical median nerve stimulation at the wrist, C3′ *vs* Fz during baseline (1, awake), during anaesthesia (2), and during recovery (3). Different latency peaks are indicated. (Upper traces) Patient AC, 50 yr, anaesthesia with isoflurane/nitrous oxide, no memory for immediate recovery (Middle) Patient KE, 42 yr, anaesthesia with isoflurane/nitrous oxide and implicit memory. (Lower traces) Patient RR, 49 yr, anaesthesia with propofol/sufentanil and explicit memory.

Clinical measurements

There was no difference among the three memory groups in their physical characteristics (Table 3) or the clinical measurements between the three memory groups at AWAKE, ANAESTH, or RECOVERY. The time of extubation and RECOVERY, when the patients opened their eyes spontaneously, did not differ among the groups. In contrast, the time of anaesthesia was significantly less in the patients of the group EXPLICIT (mean 88 (SD 32) min) than in the group IMPLICIT (113 (40) min), and the group NO-MEM (112 (28) min; Table 2).

Additional opioid dose did not differ among the groups. The total amount of opioid for the different memory groups was: fentanyl (mg kg^{-1} h^{-1}; in combination with isoflurane): group NO-MEM: 0.019 (0.001) (n=7); group IMPLICIT 0.021 (0.001) (n=8); group EXPLICIT 0.022 (0.001) (n=14); P=0.643. For sufentanil (µg kg^{-1} h^{-1}; in combination with propofol): group NO-MEM: 0.45 (0.15) (n=8); group IMPLICIT 0.35 (0.07) (n=3); group EXPLICIT 0.43 (0.06) (n=9); P=0.387. In the patients who received isoflurane, the end-tidal isoflurane concentration did not differ between the three groups at RECOVERY.

Discussion

We found that spontaneous recall for recovery was impaired in 53% of patients after general anaesthesia. The information, which was recalled 24 h post-operatively, was not the same for all patients. Some patients remembered a shown object, others the electrical stimulation of the median nerve or the face mask. Twenty-two per cent of the patients had implicit memory function. The mid-latency MnSSER components P45 and N50 and the inter-wave conduction time LatN35 – LatP45 were significantly shorter in the patients who had explicit memory than in the patients, who did not have any memory. However, the MnSSER data did not differ among the patients with or without implicit memory formation.

We wished to assess in a descriptive way the recovery of memory and MnSSER changes in clinical circumstances. We cannot attribute our findings to a single anaesthetic substance or anaesthetic regimen, because the statistical power to evaluate this question is low (three memory groups, two anaesthetic regimens). However, all the patients were pre-medicated with midazolam, a substance to be amnesic.[7] A more pronounced effect would have been expected in the patients in whom the total time of anaesthesia was shorter. In contrast, these patients especially, had explicit memory in the present study. Therefore, we concluded that midazolam did not affect our results.

The total time of anaesthesia was significantly shorter in the patients who had recall. Because the infusion rate for propofol and the concentration of isoflurane were fixed, the total quantity of anaesthetic increased with the duration of anaesthesia. Therefore, most probably residual anaesthetic

Table 2 Statistical results analysis of variance (between and within subject designs) for MnSSER latency components, inter-peak latencies and amplitudes including AWAKE and RECOVERY

	F	Hypoth. DF	Error DF	Significanc of *F*
(A) Latencies				
Latencies	224.10	4	40	0.000
Time	1103.33	1	43	0.000
Memory	3.34	2	43	0.045
Latency/time	108.47	4	44	0.000
Latency/memory	2.09	8	78	0.047
Time/memory	4.11	2	43	0.023
Latency/time/memory	5.23	8	172	0.000
(B) Inter-wave conduction times				
Inter-wave CT	40.18	4	29	0.000
Time	394.03	1	32	0.000
Memory	5.88	2	32	0.007
Inter-wave CT/time	26.77	4	29	0.000
Inter-wave CT/memory	2.23	8	56	0.038
Time/memory	7.07	2	32	0.003
Inter-wave CT/time/memory	2.61	8	128	0.011
(C) Amplitudes				
Amplitudes	4.79	3	40	0.006
Time	13.05	1	42	0.001
Memory	0.16	2	42	0.850
Amplitudes/time	9.70	3	40	0.000
Amplitudes/memory	0.34	6	78	0.913
Time/memory	0.77	2	43	0.471
Amplitudes/time/memory	0.79	6	126	0.583

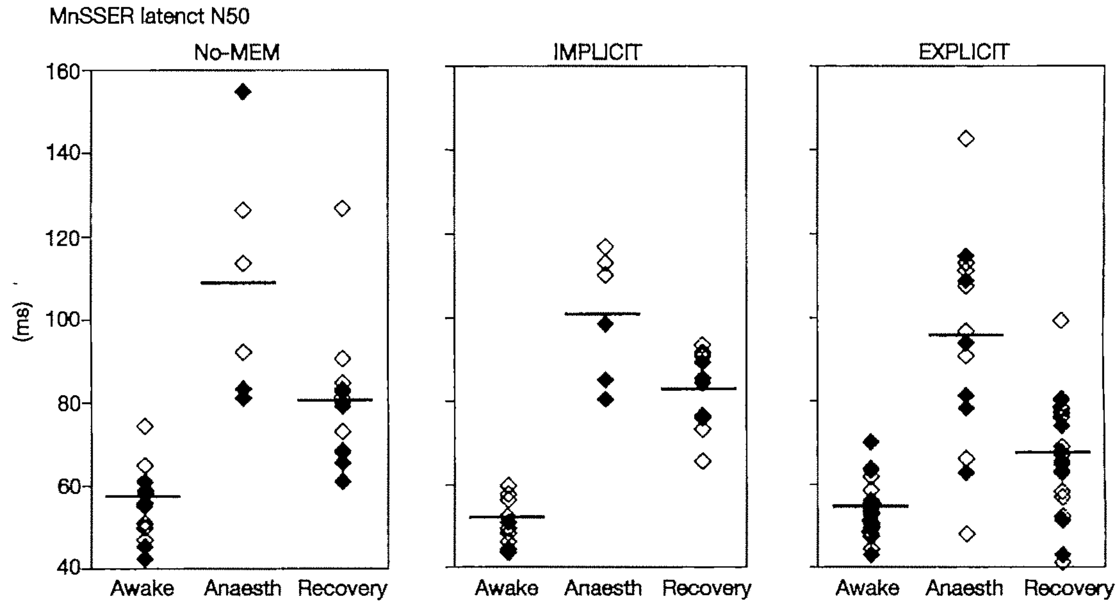

Fig 2 MnSSER amplitudes N50 of individual subjects with bars indicating the means are shown Group NO-MEM (*n*=15) without memory, group IMPLICIT (*n*=11) with implicit memory and group EXPLICIT (*n*=23) with explicit memory for the immediate wake-up phase from anaesthesia. White symbols, isoflurane/nitrous oxide; black symbols, propofol/sufentanil N50 was suppressed completely during anaesthesia in 22 patients.

agents would be different in the patients and affect memory performance. The chosen clinical endpoint of the patients' responsiveness, that is that all patients were able to recognize and verbally define a shown object, did not allow prediction of the patients' memory. Dutton and colleagues[8] found no evidence of memory formation in 13 out of 28 patients, as long as the patients did not sustain wakefulness sufficiently long enough to complete four hand squeezes. Unfortunately we did not test this clinical sign.

The latency of the primary cortical complex of the tibial nerve SSER is changed by high doses of fentanyl and sufentanil.[9] In the present study the time of the last dose and amount of opioids given per hour did not differ between the groups. Although the effect sizes of the group differences

Table 3 Mean (SD) for MnSSER latency components (in seconds) before anaesthesia (AWAKE), during anaesthesia and during recovery from anaesthesia. Group NO-MEM without memory, IMPLICIT with implicit memory and EXPLICIT with explicit memory for the immediate wake-up period

Group	Time	N20	P25	N35	P45	N50
(A) After isoflurane anaesthesia (n=29)						
NO-mem (n=7)	AWAKE	19.0 (0.7)	23.1 (2.2)	34.0 (4.7)	43.6 (7.9)	60.4 (8.9)
	ANAESTH	21.7 (3.0)	28.9 (5.9)	46.9 (11.5)	82.4 (24.9)	104 (19.7)
	RECOVERY	20.1 (2.8)	25.3 (4.5)	38.4 (5.8)	63.5 (12.0)	88.7 (20.8)
Implicit (n=8)	AWAKE	19.1 (0.7)	24.5 (3.1)	32.4 (5.4)	39.4 (5.9)	53.8 (5.2)
	ANAESTH	21.0 (1.0)	27.2 (2.8)	44.3 (12.3)	71.2 (17.0)	107.2 (14.4)
	RECOVERY	19.6 (0.9)	25.5 (1.5)	37.6 (3.5)	55.6 (7.7)	83.2 (10.8)
Explicit (n=14)	AWAKE	18.9 (1.0)	23.9 (2.7)	32.0 (3.0)	40.0 (4.7)	53.4 (6.2)
	ANAESTH	20.7 (1.6)	26.4 (3.5)	41.6 (10.0)	71.3 (24.6)	97.0 (32.2)
	RECOVERY	19.3 (1.0)	24.6 (2.1)	35.1 (4.3)	49.3 (9.7)	71.2 (13.6)
(B) After propofol anaesthesia (n=20)						
NO-mem (n=8)	AWAKE	20.0 (1.0)	25.3 (2.6)	32.6 (4.2)	40.8 (4.0)	54.0 (7.3)
	ANAESTH	22.7 (1.9)	29.6 (3.4)	46.1 (6.6)	60.0 (6.8)	119.0 (32.1)
	RECOVERY	21.8 (0.8)	25.8 (2.1)	35.8 (2.6)	50.3 (4.5)	85.2 (9.0)
Implicit (n=3)	AWAKE	20.4 (1.1)	23.8 (0.6)	32.7 (1.4)	37.6 (2.0)	47.1 (4.1)
	ANAESTH	22.0 (1.3)	25.3 (1.4)	37.7 (5.3)	61.7 (7.5)	90.3 (12.7)
	RECOVERY	21.5 (1.7)	24.3 (2.2)	37.6 (3.2)	52.8 (3.4)	84.1 (6.7)
Explicit (n=9)	AWAKE	19.2 (0.8)	24.2 (2.1)	30.9 (3.9)	39.9 (5.6)	55.0 (9.5)
	ANAESTH	20.8 (1.2)	25.8 (3.3)	36.1 (5.4)	65.3 (11.1)	93.7 (19.2)
	RECOVERY	19.9 (0.8)	24.5 (1.6)	34.1 (3.1)	45.1 (7.1)	63.5 (11.9)

Table 4 Physical characteristics and clinical measurements (*P<0.01)

	No-MEM (n=15)	IMPLICIT (n=11)	EXPLICIT (n=23)
Age (yr) [range]	47 (12) [22–67]	38 (14) [18–56]	39 (10) [19–55]
Weight (kg)	67 (13)	69 (13)	68 (16)
Length (cm)	166 (8)	166 (10)	169 (8)
Anaesthesia (min)	112 (28)	113 (40)	88 (32)*
Extubation (min)	17 (8)	13 (5)	14 (5)
Recovery (min)	25 (9)	24 (4)	24 (7)

found in the present study do not suggest any clinical relevance, further studies are needed to exclude the effects of opioids on memory performance and/or MnSSER changes.

Our findings support data from volunteer studies, that memory is impaired by subanaesthetic concentrations, when responses to command are still present. Dwyer and colleagues[10] showed in 12 healthy volunteers that conscious as well as unconscious memory was completely suppressed at 0.45 MAC isoflurane, while 0.6 MAC nitrous oxide suppressed conscious memory only. Veselis and colleagues[11] found a marked reduction in short-term memory capacity and dramatically impaired free recall and recognition during a low-dose infusion of propofol (75 $\mu g\ kg^{-1}\ min^{-1}$) in 10 volunteers.

We found selective uptake of sensory information in patients during emergence from anaesthesia. The human brain contains at least five anatomically distinct networks involved in sensation to cognition,[12] but we do not know how anaesthetics act on the different systems of memory formation. Block and co-workers[13] found different effects of nitrous oxide on psychophysical tests involving declarative or procedural memory. Alkire and colleagues[14] demonstrated in PET-studies, that anaesthetic effects are not uniformly distributed in different brain areas. In the present study the MnSSER components P45 and N50 differed between the patients with and without explicit memory, whereas the earlier components did not. Different parts of the brain are responsible for the MnSSER components.[15 16] The parts that form P45 and N50 could be affected in the same way as the neurons which are involved in memory formation, so that impairment of memory formation and changes of MnSSER components occur simultaneously. It is unlikely that MnSSER changes directly reflect memory formation of other sensory systems, like the visual system, which was activated in memory processing for the shown object.

Evidence suggests that EEG measures may suggest the likelihood of memory formation intra-operatively. Liu and colleagues found that the bispectral index, a variable derived from the spontaneous EEG, correlated with intra-operative picture recall during propofol bolus injection.[17] In patients having cardiac surgery, an increase of the AER latency Pa of greater or less than 12 ms distinguished among patients with and without implicit memory post-operatively.[18] Some recognition of an auditory stimulus may be related to other potentials (P300) intra-operatively.[19 20] In the present study the MnSSER measurements were not related to implicit memory formation. However, the experimental design, gave a chance of 20% of guessing the shown object from the four distractor objects. This might have suggested a greater number of patients with implicit memory than really existed and may have confused this measure of memory.

In conclusion, we found that the MnSSER component P45 and N50 were prolonged when post-operative recall was absent during recovery from general anaesthesia. However, sensitivity and specificity are not sufficient to recommend MnSSER as a measurement for everyday clinical routine. More research is needed to show if MnSSER components indicate memory during surgical anaesthesia.

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Noise in the postanaesthesia care unit

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Background. Although the postanaesthesia care unit (PACU) can be noisy, the effect of noise on patients recovering from anaesthesia is unknown. We studied the sources and intensity of noise in the PACU and assessed its effect on patients' comfort.

Methods. We measured noise in a five-bed PACU with a sound level meter. Noise levels were obtained using an A-weighted setting (dBA) and peak sound using a linear scale (dBL). Leq (average noise level at 5-s intervals), maximun Leq (LeqMax), minimum Leq (LeqMin) and noise peaks (Lpc) were calculated. During recording, an independent observer noted the origin of sounds from alarms and noise above 65 dB intensity (P65dB). Two hours after leaving the PACU, patients were asked about their experience and to rank their complaints on a visual analogue scale (VAS) using unstructured and structured questionnaires.

Results. We made 20 187 measurements over 1678 min. The mean Leq, LeqMax and LeqMin were 67.1 (SD 5.0), 75.7 (4.8) and 48.6 (4.1) dBA respectively. The mean Lpc was 126.2 (4.3) dBL. Five per cent of the noise was at a level above 65 dBA. Staff conversation caused 56% of sounds greater than 65 dB and other noise sources (alarm, telephone, nursing care) were each less than 10% of these sounds. Five patients reported disturbance from noise. There was no significant difference in Leq measured for patients who found the PACU noisy and those who did not [59.5 (3.1) and 59.4 (2.4) dBA respectively]. Stepwise multiple logistic regression indicated that only pain was associated with discomfort.

Conclusions. Even though sound in the PACU exceeded the internationally recommended intensity (40 dBA), it did not cause discomfort. Conversation was the most common cause of excess noise.

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The National Institute for Occupational Safety and Health (NIOSH) recommend that the noise intensity in hospitals should not exceed 35 dBA (A-weighted setting) during the night and 40 dBA during the day.[1] Excess noise can have adverse physiological and psychological effects on patients and increase mistakes by medical personnel.[2 3] Although attention has been focused on noise in intensive care[4–6] and during major surgery,[2 7 8] postanaesthesia care units (PACU) are also noisy places.[9 10] Noise can come from ventilators, monitors, alarms and other apparatus and can also spread from adjacent areas such as the operating theatre, the transfer area and scrub-up areas. Because patients in the PACU are often sedated or anaesthetized, noise is usually ignored. However, noise can affect anaesthetized patients or animals during arousal.[11–13] Although the sources and extent of noise are known, the effect of noise on patient comfort is not clear.

We set out to determine the causes of noise in the PACU and to quantify the contribution of noise, compared with other factors, to patient discomfort.

Material and methods

The study was conducted after approval from our Institutional Review Board. Patient consent was not required because the procedure was observational We performed a prospective study of 26 patients having elective general surgery under general anaesthesia in a 35-bed, university-based teaching department. Operating room and recovery room staff worked without changing their normal practice.

The 9×3.5 m PACU was an open ward with five beds close to the operating theatre (three rooms). Noise level was measured when there were at least four patients in the

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PACU. All measurements were made between 8.00 a.m. and 1.00 p.m. The PACU opened onto a corridor by a door that remained open. Each bed in the PACU was equipped with a ventilator, a bedside monitor with ECG, pulse oximetry and non-invasive arterial blood pressure measurement, and two motor syringe pumps. At least 12 alarms were set for each patient. During the study period, one or two nurses worked in the unit. Personnel working in this area were informed of the study but no attempt to control noise was made before the beginning of this study.

Sound monitoring

Sound levels were measured in dBA. Noise was measured with a frequency filter called the A-weighting network. This filter correlates well with the human response to noise because it attenuates low-frequency sound by an amount that corresponds to the sensitivity of the human ear. We used a sound level meter with internal storage (model SIP 95 S; Essilor, Créteil, France). This sound meter incorporates a type-1 microphone and records sound ranging from 40 to 140 dBA. The sound meter was calibrated before the study (acoustic calibrator; Essilor). For the accurate measurement of what the patient would be hearing, the sound meter was placed close to the patient's head. An observer sat next to the head of the patient and noted the source of sounds that had peak values greater than 65 dBA (P65dB). During recording, the noise level was monitored continuously. The sound meter sampled peak sound every 125 ms (Lp) and produced an integrated pressure sound level each 5 s (Leq). An interval of 5 s was chosen as the being the time an observer was expected to require in order to identify a given sound. The stored data were downloaded to an IBM computer for data analysis using commercial software (Alsono; Aclan, Toulouse, France). The following values were derived: Leq (5-s period), maximum Leq (LeqMax), minimum Leq (LeqMin), maximum peak (LpcMax, expressed in dBL). The software also calculated the sound pressure level that included 50 or 90% of peak sound collected (LE 50 and LE 90 respectively).

Patient experience of time in the PACU

Fitness for discharge was determined with an Aldrete score. Two hours after discharge, the patients were interviewed and asked to assess their experience of the unit. Two questionnaires were completed with the help of one of the investigators. The first questionnaire was unstructured (spontaneous complaints, indirect questions). The second was a structured questionnaire asking about common complaints, such as pain, cold, nausea and vomiting, nursing care, light and specifically noise. The patient rated each item in the questionnaire on a visual analogue score (VAS) from 0 to 10 and classified their experience in the unit as stressful or not. VAS values greater than 3 were considered clinically significant.

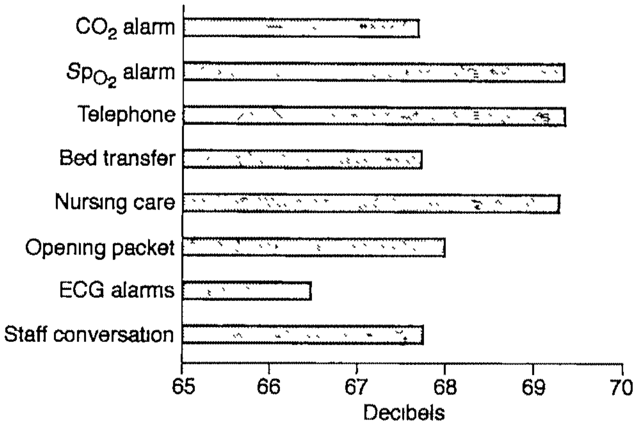

Fig 1 Mean intensities of different noises recorded in the PACU

Statistics

Results are expressed as mean (SD or range). When appropriate, groups were compared using the Mann–Whitney *U* test. Univariate analysis was done with a statistical program (Statview; Abacus, Berkeley, CA). Significant complaints were incorporated into a stepwise multiple logistic regression to describe the relationship between patient satisfaction and complaints. A *P* value less than 0.05 was considered statistically significant.

Results

We studied 26 adult patients (14 female, 12 male). Surgical procedures included urology and dental, abdominal and plastic surgery. Mean age was 45 yr (range 19–78 yr).

We made 20 187 measurements over 1678 min of recording. Mean (SD) recording time per patient was 55 (22) min.

The mean integrated sound pressure level (Leq) was 67.1 (5.0) dBA. The maximum and minimum values of this variable were 75.7 (4.8) and 48.6 (4.1) dBA respectively. The mean peak level (Lpc) was 126.2 (4.3) dBL. The LE 50 was 55.9 (3.0) dBA and LE 90 was 52.1 (3.3) dBA.

The intensities of some of the noises are shown in Figure 1. Five per cent of the noises were above 65 dBA (1074 peaks). Staff conversation caused 56% of P65dB; other noise sources (alarm, telephone, nursing care) were each less than 10% of P65dB (Fig. 2). None of the alarm sounds was related to a critical medical event.

Eleven patients reported discomfort during their stay in the unit. Most spontaneous complaints were about pain (six patients) and noise (two patients). The structured questionnaire identified pain (10 patients; 38%), nursing care (10 patients; 38%), cold (nine patients), oxygen face mask (seven patients) and noise (five patients; 19%) as important factors (VAS>3). The mean VAS was less for noise [4.8 (1.9)] than for other sources of patient discomfort (Table 1). Conversation rather than alarms was the major source of complaint about noise in these five patients (4 *vs* 1). There

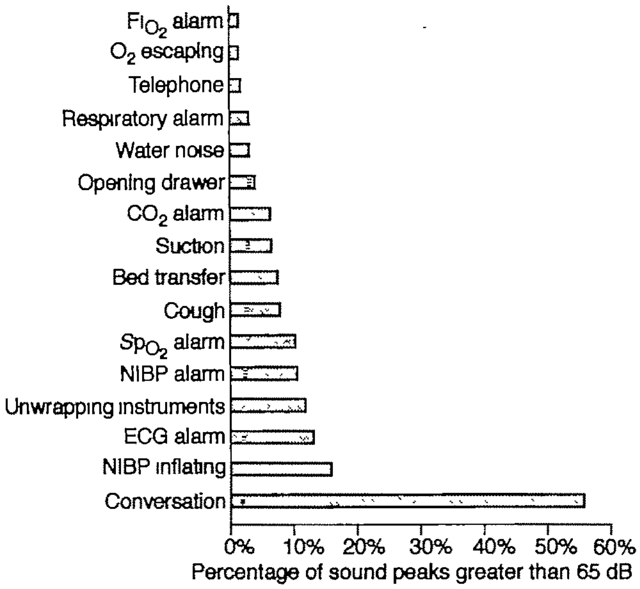

Fig 2 Origin of peaks above 65 dB recorded in the PACU (%). For clarity, noises with frequency less than 2% are not shown.

was no significant difference in mean sound level measured for patients who found the PACU noisy and those who did not [59.5 (3.1) and 59.4 (2.4) dBA respectively].

Logistic regression analysis identified pain as the only factor affecting patient discomfort in the PACU (Table 2).

Discussion

In the past, patient satisfaction in the PACU has been related to the quality of nursing care and the control of side-effects after anaesthesia and surgery. However, factors such as light intensity, ambient temperature and prevention of infection by air filtration and from water pollution can affect patient perception of care.[8 14] We found that noise can be a relevant environmental factor but it is not the main cause of discomfort.

Several studies have shown that hospitals are noisy. In the operating theatre, the average noise level is in the range of 60–65 dBA.[2 7 8] Noise in the intensive care unit (ICU) is often greater than that recommended by NIOSH. Soutar and Wilson[15] found an average sound level of 66 dBA and Balogh and colleagues[4] reported values between 60 and 65 dBA in a four-bed ICU with noise levels above 65 dBA during teaching. Others found noise intensities between 50 and 75 dBA.[16 17] In the PACU, a study by Minckley[18] identified the sources of noise and found average sound levels ranging from 50 to 70 dBA, and Liu and Tan[10] showed that the mean noise level in the PACU could reach 72 dBA. We found the average noise level in our PACU to be 67 dBA. Differences in noise levels may be caused by features of a PACU that affect noise reflection and intensity. Noise is also affected by the amount and type of equipment that is being used. The type of surgery and the level of care needed may also influence noise.

Table 1 Results of the structured questionnaire about complaints The 26 patients rated each item with a visual analogue score (VAS) Score 1 is the mean VAS (SD) calculated for all patients; score 2 is the mean VAS (SD) calculated only for patients with VAS>3. n d.=not done

	Number of patients	**Score 1**	**Score 2**
Pain	10	2.8 (2.8)	5.6 (2.2)
Gastric suction drainage	10	2.4 (3.2)	5.8 (2.6)
Cold	9	2.4 (2.9)	5.0 (2.5)
Oxygen mask	7	1.9 (2.4)	4.9 (2.0)
Noise	5	1.2 (2.1)	4.8 (1.9)
Nausea	1	n d	n.d.
Retching	0	n d.	n.d.
Hungry	2	n d.	n.d

Table 2 Relationships (stepwise logistic regression) between patient satisfaction and different complaints in the PACU. Only complaints with a *P* level <0.25 in a univariate analysis were entered in the model

Complaint	**Odds ratio**	**Lower 95% confidence limit**	**Upper 95% confidence limit**	***P***
Pain	9.4	1.0	82.3	0.04
Cold	0.44	0.05	4.30	0.48
Drainage	3.80	0.38	38.12	0.25
Noise (dB)	1.08	0.76	1.54	0.66
Peaks >65 dB	1.02	0.89	1.16	0.76

Most noises (95%) were in the 50–65 dB range, a level classified as 'ambient'. Leq is the mean noise level over a period of time. In contrast, Lpc is recorded at 0.125 ms intervals and represents peak noise. Lpc as high as 130 dB was recorded, a noise level close to that from an aeroplane. Staff conversation was responsible for most of the peaks above 65 dB, and conversation was an important source of complaint in patients who reported that the PACU was noisy. This observation supports previous reports that most noise in operating theatres and ICUs is caused by workers, levels being 70–80 dB.[2 8] Even though conversations between workers in the PACU are important for patient care, high sound levels should be avoided and conversations in the PACU should be restricted to essential matters.

Other noises come from equipment alarms,[19] mainly Sp_{O_2}, NIBP and ECG devices. None of these noises caused a potentially serious problem and they arose mainly as a result of patient movement. Both alarms represented 23% of peak above 65 dB, a value close to the 25% reported by Kahn and colleagues.[16] Most alarm sounds are related to non-critical events and were reported to account for 99.5% of the total of 1455 alarms recorded over a 3-week period in an ICU.[20] An important source of noise in the PACU is false alarms, and we agree with others that a graded and intelligent system of alarms might help to distinguish life-threatening events from unimportant disturbances.[21] This would improve monitoring and reduce noise from false alarms.

Noise can distress 30% of patients in a PACU,[10] but individual perception is important. We found that those who were distressed by noise were not exposed to sound levels that were any greater than those who did not find the unit noisy. Regression analysis did not show that noise was generally a factor causing discomfort. As in the ICU,[22] some patients recovering from anaesthesia may have found some noises reassuring rather than alarming.

Pain remains the major cause of discomfort in our unit despite treatment plans for pain management. The need for pain therapy was not recorded in this study because the type of surgery was not standardized. Minckley found that when noise levels were high (60–70 dB) the number of patients given analgesics increased.[18] However, sound levels were measured at half-hourly intervals, were not measured for each patient, and the type of medication given was not described. In awake patients, music decreased patient-controlled sedative and analgesic requirements.[23] Patients in the control group in this study did not use a headset, so the reduced requirements for treatment could have been caused either by music or by reducing the effect of ambient noise. Whether noise in the PACU pain perception and analgesic requirements needs further study.

Noise is also a source of stress for staff because noise impairs concentration and mental efficiency.[24 25] Noise is an important stressor of ICU nurses, though the health hazard is not easy to prove.[26 27] Bayo and colleagues[28] interviewed hospital workers and found that noise interfered with their work and could cause mental fatigue, headaches and hypertension. Even if noise is not an important cause of discomfort for patients, health-care workers should be protected from excessive noise.

Noisy situations can mask vital alarms.[29] Verbal communication may also be impaired, even at noise levels that do not reduce intelligibility. The reliability of oral communication can be assessed by calculating preferred speech interference levels.[30] The value of 67 dB for sound pressure obtained in our study suggests that communication may be hampered and unsatisfactory at this level.[2 30]

There are some limitations in this study. The study was performed in a small unit and the findings may not be applicable to large units. However, noise levels seem to be similar in three-, four- and six-bed ICUs. Different patients and surgical procedures might show different effects, but this has not been found in previous studies.[10 31] The staff of the unit were aware of the study because an observer was sitting close to the patient, but we could not find a means of avoiding this bias before data collection. Data collection was complex because the source of many noises had to be recorded simultaneously by the observer. This could not be achieved by video recording because this would not distinguish noise from different origins, and explains why observers have been used to identify the sources of noise in previous studies.

Conclusion

We conclude that high noise levels were present in the PACU and that most of these noises could be prevented. However, noise was not perceived as the main cause of discomfort by patients. The influence of noise on the quality of care and the performance of staff needs further study.

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Remifentanil by patient-controlled analgesia compared with intramuscular meperidine for pain relief in labour

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Background. The pharmacokinetics of remifentanil suggests that it may be suitable for analgesia during labour.

Methods. In an open pilot study, 36 women requesting meperidine for analgesia were recruited early in labour and randomized to receive either meperidine i.m. or remifentanil given as patient-controlled analgesia (PCA). Pain severity, sedation and anxiety were assessed with visual analogue scales and overall effective analgesia was assessed by the woman and midwife.

Results. The pain scores were lower in the remifentanil group: median pain score at 60 min was 72 mm for meperidine and 48 mm for remifentanil (P=0.004) and median maximum pain score during the first 2 h was 82.5 mm for the meperidine group and 66.5 mm for the remifentanil group (P=0.009). Both the midwives' and the women's assessments of overall effective analgesia were higher in the remifentanil group [Likert scale (5 = excellent to 1 = poor): χ^2=12.10, P=0.002 for mothers' assessment; χ^2=12.80, P=0.002 for midwives' assessment].

Conclusion. In this pilot study, remifentanil by PCA gave better pain relief to mothers in labour than intramuscular meperidine. However, remifentanil is a potent respiratory depressant and adequate continuous monitoring is necessary.

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Most women who deliver in modern obstetric units request some form of pharmacological pain relief. There are many treatment options available to relieve the pain of childbirth. Some are more effective than others. Non-pharmacological forms of analgesia, such as breathing exercises and transcutaneous nerve stimulation, can be inadequate for established and augmented labour. Entonox may also be inadequate. Epidural analgesia offers the best pain relief for many women in labour. If an epidural is contraindicated or a woman does not wish to have an epidural, meperidine is the main alternative but, although widely used, it is a poor analgesic and the main effect is sedation.[1 2]

Remifentanil's rapid onset and offset of effect[3 4] should make it an ideal drug for the intermittent painful contractions of labour. It has been used as an i.v. infusion during non-urgent Caesarean section as an adjunct to epidural anaesthesia. It does cross the placenta (mean uterine vein:maternal artery ratio=0.88) but is rapidly metabolized, redistributed or both (mean uterine artery:uterine vein ratio=0.29), with no clinically adverse effects on the neonate.[5]

Patient-controlled analgesia (PCA) techniques are not new to obstetrics: PCA is the standard delivery system for Entonox. Meperidine,[6] butorphanol tartrate,[7] tramadol,[8] nalbuphine[9] and fentanyl[10 11] have all been given by PCA in labour. Remifentanil may have an advantage compared with these because of its rapid onset time and rate of hydrolysis. There are case reports of remifentanil PCA in labour in parturients with known platelet abnormalities.[12 13] Intravenous PCA should be better than intermittent i.m.

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Table 1 Patient details before start of analgesia

Variable	Meperidine (n=18)		Remifentanil (n=18)	
	Median	Interquartile range	Median	Interquartile range
Age	29	25–30	28	22–32
Weight	64	58–76	66.5	58–78
Height	165	163–170	160	157–168
Gestation	39.6	39–40	40.1	39.25–41
Dilation	4	3–5	3	3–4
Pain score	68	59–76	71	51–82
Sedation	43	15–54	31	18–74
Anxiety	49.5	31–74	66	45–77
Systolic blood pressure	120	114–130	127.5	120–140
Diastolic blood pressure	80	70–84	71	70–80
Pulse rate	77.5	74–81	89	75–92
Respiratory rate	20	18–24	20	20–24
Sa_{O_2}	97	97–98	97	97–98

injections because it avoids the pain of injection and allows better matching of analgesic delivery to the pain.

We conducted an open randomized pilot study to compare the analgesic effect of remifentanil given as PCA with i.m. meperidine during labour.

Methods

After local ethics committee approval, we recruited women aged between 18 and 40 years, of mixed parity, between 38 and 42 weeks gestation in early labour. Women weighing less than 50 kg or more than 100 kg were excluded. After they had given written informed consent, women were assigned randomly to one of two groups by sequentially numbered, sealed opaque envelopes prepared by an independent practitioner. Patients in group M were assigned i.m. meperidine 100 mg and an antiemetic and those in group R were assigned i.v. remifentanil via PCA (20 μg bolus over 20 s, 3 min lockout and no background infusion); full instructions were given to the mother and attending midwife. A dedicated i.v. cannula was sited in a forearm vein in women in group R. A dosing study was conducted before the study proper to ascertain the dose and lockout period required to relieve the pain of labour without obvious clinical side-effects. Starting with a 5 μg bolus, an increasing dose of remifentanil was given at the beginning of each painful contraction until the contraction was pain-free, and the time to the next painful contraction was noted.

Pain was assessed with a continuous visual analogue scale (VAS; 100 mm, marked 'no pain' to 'worse pain imaginable'). Women were asked to mark on the line the worst pain they had felt during their last contraction after it had finished. Sedation and anxiety were assessed similarly, using the terms 'wide awake' to 'very sleepy' for sedation, and 'very calm' to 'very anxious' for anxiety. Nausea scores and the physiological variables of blood pressure, pulse rate, ventilatory rate and oxygen saturation by pulse oximetry were also measured.

Baseline recordings were made and then measurements were taken every 30 min after analgesia was started. Although measurements were recorded every 30 min, all women were observed throughout by their attending midwife, and one of the investigators was available in the delivery suite at all times during the study. All patients were monitored by continuous pulse oximetry.

If the assigned analgesia was inadequate for the patient at any time, an alternative was offered and further study recordings were discontinued.

The foetus was monitored by continuous cardiotocography and Apgar scores were noted at delivery. All women had access to Entonox at all times.

The overall effective analgesia was rated after delivery by the mother and attending midwife within 2 h of delivery on a five-point verbal scale ranging from excellent to poor (Likert scale: 5=excellent, 4=very good, 3=good, 2=fair, 1=poor).

A power calculation was performed at the design stage of the study. We estimated that the probability of a woman who was receiving remifentanil reporting a lower pain score than a woman receiving meperidine was 0.85. Assuming that the pain scores would be compared using a Wilcoxon rank sum test, for a two-sided 5% level of statistical significance and 90% power we estimated that we needed to recruit 30 patients in total, 15 in each group.

The overall effective analgesia rating (Likert scale) was analysed using the χ^2 test. Fisher's exact test was applied to the nausea and vomiting scores and epidural conversion rates. The combined influence of drug treatment and other postrandomization events was assessed by analysis of variance. All other non-parametric data were compared using the Wilcoxon rank sum test. Parametric data were analysed with the t-test. Analysis was performed using Stata for Windows (Stata Corporation, Texas, USA) and Microsoft Excel for Windows.

Results

Forty-one women were asked to take part in the study. Five women refused, stating that they preferred to have

Table 2 Details of labour. *Data incomplete or missing from notes

Variable	Meperidine (*n*=18)		Remifentanil (*n*=18)	
	No.	**%**	**No.**	**%**
Parity				
1	13	72	13	72
2	3	17	0	0
3	2	11	3	17
4+	0	0	2	11
Spontaneous onset of labour	15/17*	88	16/18*	89
Artificial rupture of membranes	8/16*	50	9/18	50
Syntocinon infusion used	6/17*	35	5/17*	29
Entonox used	13/16*	81	10/18	56
Fetal position				
OA	9/11*	82	4/12*	33
OP	2/11*	18	4/12*	33
OL	0/11*	0	1/12*	12
T	0/11*	0	3/12*	25
Type of delivery				
Spontaneous vaginal	16/17*	94	11/18	61
Ventouse	1/17*	6	4/18	22
Caesarean section	0/17*	0	3/18	17

Table 3 Pain scores at 60 min and maximum pain scores during the first 2 h after analgesia commenced. *Significant

	Meperidine		Remifentanil		*P*
	Median	**Interquartile range**	**Median**	**Interquartile range**	
At 1 h	72	62–80	48	22–50.5	0.0004*
Max. score over 2 h	82.5	75–90	66.5	57–78	0.009*

meperidine. Thirty-six patients were recruited and there were no withdrawals. Eighteen patients were randomized to each treatment group (Table 1). The number of primigravid patients in each group was similar (13/18 in each group). Details of labour in the two groups are summarized in Table 2.

The pain scores at 60 min and the maximum pain scores during the first 2 h after analgesia commenced were significantly lower in the remifentanil group (Table 3).

There was no difference in Entonox usage between the two groups (*P*=0.11).

There was no difference between the two groups in the pain scores at 1 h or maximum pain score over the first 2 h in relation to artificial rupture of membranes (*P*=0.86, *P*=0.31) or Syntocinon usage (*P*=0.77, *P*=0.35).The midwives' and mothers' assessments of 'overall effective analgesia' were both higher in the remifentanil group (*P*=0.002) (Figs 1 and 2). There were no other significant differences between the two groups.

For two women receiving meperidine and seven receiving remifentanil, haemoglobin oxygen saturations of less than or equal to 94% were recorded. The lowest for meperidine was 89% and the lowest for remifentanil 92%. The minimum saturation did not differ significantly between the two groups (*P*=0.08) but the impression was that the overall saturation may have been lower for women receiving remifentanil.

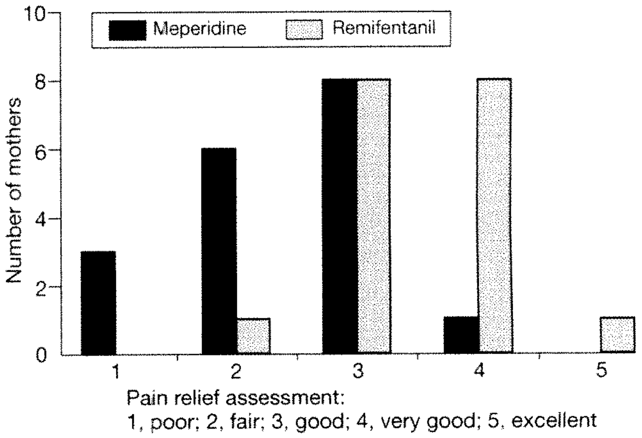

Fig 1 Midwife's assessment of overall effective analgesia. Significantly better in the remifentanil group (*P*<0.002).

There was no significant difference in the recorded minimum ventilatory rate between the two groups (*P*=0.60), although rates less than 8 between contractions were recorded for three patients receiving remifentanil; these responded quickly to verbal stimulation.

All women receiving meperidine were given an anti-emetic at the same time (promethazine 25 mg or

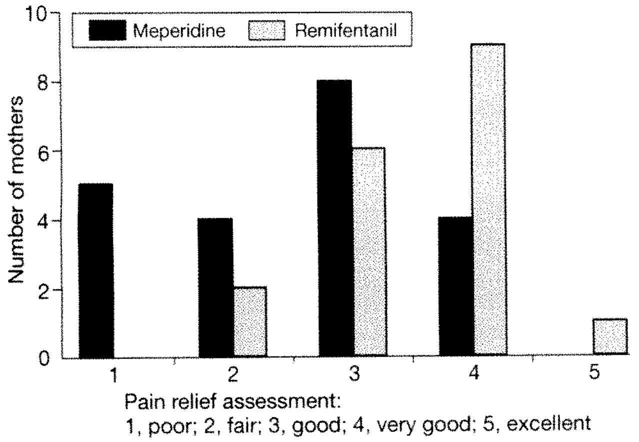

Fig 2 Mother's assessment of overall effective analgesia. Significantly better in the remifentanil group ($P<0.002$).

prochlorperazine 12.5 mg). No antiemetic was given to women receiving remifentanil unless indicated clinically. Ten women receiving meperidine and five receiving remifentanil experienced nausea and vomiting ($P=0.06$). Three women receiving remifentanil went on to receive an antiemetic (either promethazine 25 mg or prochlorperazine 12.5 mg).

Three women receiving meperidine later received an epidural, while seven receiving remifentanil required additional analgesia and later an epidural ($P>0.05$).

There were more non-spontaneous vaginal deliveries in the remifentanil group ($P=0.04$). The three Caesarean sections in the women receiving remifentanil were not related in time to the use of remifentanil and all three women needed epidural analgesia because of inadequate pain relief. The time to section after the epidural was sited was between 2 and 8 h. Three of the four ventouse deliveries in the women receiving remifentanil were not related in time to the use of remifentanil and all three women needed epidural analgesia because of inadequate pain relief. The time to ventouse delivery after the epidural was sited was between 3 and 7 h. If this information is taken into account, there would be one non-spontaneous vaginal delivery in each group. The results of ventouse deliveries and Caesarean sections are summarized in Table 2.

There were no differences in Apgar scores between the two groups (epidural conversions excluded).

Discussion

In this pilot study, remifentanil by PCA provided better pain relief to mothers in labour than i.m. meperidine, judged by VAS pain scores and overall assessments by mothers and attending midwives. Although pain scores were recorded every 30 min, the comparative recordings at 60 min were analysed because it was thought that this may be when i.m. meperidine would have its maximum analgesic effect. However, to ensure an effect was not missed, the maximum pain score within the first 2 h was also analysed. Pain scores after 2 h were not analysed statistically as after this time the analgesic effects of meperidine would begin to wear off, whereas the analgesic effects of remifentanil PCA would continue.

This pilot study compared two different pharmacological regimes of analgesic administration, and this may limit the usefulness of its clinical findings. Using a PCA device can improve satisfaction scores in the clinical setting and itself affect the severity of pain. When visited the following day, almost all women who had received remifentanil commented spontaneously on the controllability of the PCA, which they considered to be an advantage. PCA meperidine and remifentanil have recently been compared in labour, but poor Apgar scores in the meperidine group terminated the study prematurely.[14]

Seven women receiving remifentanil went on to have an epidural compared with three women receiving meperidine. This was an unexpected finding as pain scores were significantly lower in the remifentanil group. The difference in epidural conversion rate between the two groups was not significant, but our sample size was small. Meperidine is a sedative. This may have some influence on women requesting an epidural. In our pilot study, a fixed bolus dose of remifentanil was used. Ideally, the dose should be tailored to the individual patient and adjustments made as necessary with the progression of labour, especially as acute tolerance can develop with prolonged use of remifentanil.[15]

More women using remifentanil had lower haemoglobin oxygen saturations and some women had low ventilatory rates. Remifentanil is a potent opioid with potentially serious side-effects. It has a rapid onset, with a time to peak effect of 60–80 s.[3] From clinical observations, we suggest that the mothers must be encouraged to make a demand at the start of contractions rather than when the contractions become painful. If pressed too late, the maximum analgesic effect will occur after the peak of the contraction, along with the side-effects. It is then that ventilatory depression, if it does occur, is more likely. There must be close communication between mother, attending midwife and anaesthetist to ensure proper use of the PCA for best effect with least side-effects.

Remifentanil may be an acceptable alternative to meperidine when epidural analgesia is unsuitable. However, it is a potent respiratory depressant and adequate continuous monitoring is advisable.

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Addition of meperidine to bupivacaine for spinal anaesthesia for Caesarean section†

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Background. In a prospective, randomized, double-blind, placebo-controlled trial, we investigated the effect of adding meperidine 10 mg to intrathecal bupivacaine on the duration of early postoperative analgesia in 40 patients having elective Caesarean section under spinal anaesthesia.

Methods. Patients received intrathecal injection of 0.5% hyperbaric bupivacaine 2.0 ml plus either normal saline 0.2 ml (saline group) or 5% meperidine 0.2 ml (meperidine group). After operation, all patients were given i.v. patient-controlled analgesia using morphine.

Results. The duration of effective analgesia, defined as the time from intrathecal injection to first patient-controlled analgesia demand, was greater in the meperidine group (mean 234 min, 95% confidence interval 200–269 min) compared with the saline group (mean 125 min, 95% confidence interval 111–138 min; $P<0.001$). The 24 h morphine requirement was similar in the two groups. The meperidine group had a greater incidence of intraoperative nausea or vomiting compared with the saline group (11 *vs* 3; $P=0.02$).

Conclusion. Addition of meperidine 10 mg to intrathecal bupivacaine for Caesarean section is associated with prolonged postoperative analgesia but with greater intraoperative nausea and vomiting.

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Keywords: anaesthesia, obstetric; analgesics opioid, meperidine; analgesic techniques, subarachnoid; analgesia, patient-controlled

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Although a local anaesthetic solution may be used alone for spinal anaesthesia, opioids are commonly added. When the lipophilic opioids fentanyl and sufentanil were added to local anaesthetic, early postoperative analgesia was prolonged compared with local anaesthetic alone.[1–3] In these studies, the reported times to first postoperative analgesic ranged from 4 to 13 h.[4] For morphine, which is more hydrophilic, postoperative analgesia may extend up to 24 h.[5–7] Meperidine is an opioid of intermediate lipid solubility and is unique in having significant local anaesthetic properties.[8] It has been used as the sole agent for spinal anaesthesia for Caesarean section.[9–11] However, few data are available on the effect of adding meperidine to local anaesthetics. Therefore, the purpose of this study was to investigate the effect of adding meperidine to hyperbaric bupivacaine in patients having elective Caesarean section under spinal anaesthesia. The primary outcome measurement was the duration of early postoperative analgesia. Secondary outcomes included cumulative analgesic requirement in the first 24 h and intraoperative side effects.

Methods

After approval from the Clinical Research Ethics Committees of the Chinese University of Hong Kong and the United Christian Hospital, we recruited 40 ASA class I or II patients who were scheduled for elective Caesarean section under spinal anaesthesia in this randomized double-blind study. Patients were eligible for recruitment if they had singleton pregnancies of more than 36 weeks gestation.

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Table 1 Maternal and neonatal data (mean (SD) or number)

	Saline group	Meperidine group	*P*
Maternal characteristics			
Age (yr)	33 (6)	33 (5)	0.83
Body mass index	27.7 (3.9)	26.8 (3.7)	0.43
Parity			
0	4	2	
1	16	11	
>1	0	7	0.014
Neonatal characteristics			
Weight (kg)	3.2 (0.5)	3.2 (0.5)	0.97
Umbilical venous blood gases			
pH	7.31 (0.06)	7.33 (0.03)	0.29
$P\mathrm{O}_2$ (kPa)	3.87 (1.09)	3.94 (0.91)	0.83
Umbilical arterial blood gases			
pH	7.26 (0.07)	7.26 (0.06)	0.96
$P\mathrm{O}_2$ (kPa)	2.22 (0.75)	1.98 (0.82)	0.35

Exclusion criteria were pre-existing or pregnancy-induced hypertension, known foetal abnormality or allergy to bupivacaine or meperidine. During the preoperative visit, written informed consent was obtained and additional instruction was given on the use of i.v. patient-controlled analgesia (PCA). Patients fasted overnight and were prescribed premedication of ranitidine 150 mg orally the evening before and on the morning of operation. On arrival at the operating theatre, 0.3 M sodium citrate 30 ml was given orally and 5 min later baseline systolic arterial pressure was calculated as the mean of three measurements taken at 2 min intervals, using the oscillometric method. A 16 G peripheral i.v. cannula was then inserted and 20 ml kg^{-1} lactated Ringer's solution given as preload. A 20 G peripheral i.v. cannula was also inserted for dedicated access for PCA.

Solutions for spinal anaesthesia were prepared under sterile conditions by the anaesthetist. Two millilitres of hyperbaric 0.5% bupivacaine was drawn into a 5 ml syringe, to which was added either 0.2 ml saline (saline group) or 0.2 ml preservative-free meperidine 5% (meperidine group). The dose of 10 mg of meperidine was chosen because this dose has previously been used intrathecally for labour analgesia.[12] [13] Patients were allocated randomly to groups by selection of the uppermost envelope from a set of preshuffled envelopes containing a code. To facilitate blinding, the anaesthetist prepared two identical 1 ml syringes containing either saline or meperidine. The anaesthetist was kept blinded while the code was revealed to the scrub nurse, who selected the appropriate syringe and discarded the other. The contents of the selected syringe were then added to the bupivacaine.

After skin disinfection and infiltration with 1% lidocaine, lumbar puncture was performed with a 25 G pencil-point spinal needle at the L2–3 or L3–4 vertebral interspace with the patient in the lateral position. After free flow of cerebrospinal fluid had been confirmed, the study solution was injected intrathecally over approximately 20 s. Patients were then immediately placed supine with lateral tilt. Oxygen 4 litre min^{-1} was administered *via* a Hudson mask.

Standard monitoring was applied, including continuous pulse oximetry and ECG. Non-invasive arterial pressure was recorded each minute from the time of intrathecal injection until delivery, and then at 3 min intervals until the end of the operation. Hypotension, defined as a decrease in systolic arterial pressure to less than 90 mm Hg or a decrease of 25% from baseline, was treated with boluses of i.v. ephedrine 10 mg as required. Respiratory rate was measured as the number of carbon dioxide peaks that occurred during continuous carbon dioxide sampling via a catheter placed within the Hudson mask.

Times of skin incision, uterine incision and delivery were noted. After delivery, oxytocin 10 IU was given i.v. Apgar scores were recorded at 1 and 5 min. Samples of arterial and venous blood were taken from a double-clamped segment of umbilical cord for immediate blood gas analysis using a Ciba-Corning 850 blood gas analyser (Ciba-Corning, Medfield, MA, USA). Intraoperative pain and pruritus were assessed according to a three-point scale (0=symptom not present, 1=symptom present but not requiring treatment, 2=symptom present and treatment given on patient request). Intraoperative pain was treated with i.v. alfentanil 200 µg as required. Pruritus was treated with i.v. chlorphenamine 10 mg as required. Any instances of respiratory depression (defined as a respiratory rate of less than 12 breaths min^{-1}), shivering, or nausea or vomiting were recorded. Nausea or vomiting was treated with i.v. metoclopramide 10 mg after first excluding hypotension.

In the recovery room, PCA was made available using a Graseby 3300 PCA device (Graseby Medical, Watford, UK) that was programmed to deliver morphine as a bolus of 1 mg, with a lockout time of 8 min and no limit over time. We defined the duration of effective analgesia given by the study solution as the time from injection to the first PCA demand. Pulse rate and non-invasive arterial pressure measurements were recorded at 5 min intervals and arterial oxygen saturation was monitored continuously. The sensory level to pinprick was assessed every 30 min until regression of block to the level of T10 or below, after which patients were discharged to the ward. Duration of sensory block was defined as the time from intrathecal injection to regression of block to T10.

Postoperative ward monitoring of patients included assessment of sedation, respiratory rate, pulse oximetry and non-invasive arterial pressure every hour for 6 h and then at 2 h intervals. An anaesthetist was available at all times during the period of PCA use, with routine review of patients in the afternoon and evening of the day of operation and on the day after the operation. The time of first PCA demand and cumulative morphine consumption 2, 6 and 24 h after intrathecal injection were obtained from the electronic memory of the PCA device. Other information collected 24 h after operation included the occurrence of any side-

Table 2 Level of sensory block

Dermatome	Saline group (*n*=20)	Meperidine group (*n*=20)
C4	0	1
C5	1	1
C6	0	2
C7	0	0
C8	0	0
T1	0	0
T2	1	3
T3	7	4
T4	7	5
T5	3	4
T6	1	0

Table 3 Incidence of adverse intraoperative events

	Saline group (*n*=20)	Meperidine group (*n*=20)	*P*
Hypotension	11 (55%)	14 (70%)	0.33
Intraoperative discomfort			
None	18 (90%)	20 (100%)	
Mild	1 (5%)	0 (0%)	
Severe	1 (5%)	0 (0%)	0.37
Shivering	8 (40%)	3 (15%)	0.16
Nausea/vomiting	3 (15%)	11 (55%)	0.02

effects in the first 24 h and any incidence of residual neurological signs.

Sample size was determined prospectively using data from previous elective Caesarean sections performed under spinal anaesthesia in our institution. Power analysis indicated that 17 patients per group were required to detect a difference of 1 h in the time to first PCA demand (α=0.05, β=0.2). Assuming a potential dropout rate of 15%, we decided to recruit 20 patients per group. Statistical calculations were performed using SPSS 9.0 (SPSS, Chicago, IL, USA). We used Student's *t*-test to analyse continuous data and the Mann–Whitney *U*-test for non-continuous data. Dichotomous data were analysed with the χ^2 test. Duration of effective analgesia was described using the Kaplan–Meier survival curve and analysed with the log-rank test. A value of $P<0.05$ was considered statistically significant.

Results

We obtained consent from 40 patients, 20 of whom were randomized to each group. Morphine consumption data were not included in the statistical analysis for one patient in the saline group because a leak in the PCA delivery system prevented accurate measurement of drug consumption. Time to first PCA demand and morphine consumption data were excluded for two patients in the meperidine group because of accidental PCA demands before the onset of pain. In the saline group, a calibration error occurred with one umbilical vein sample and sufficient umbilical arterial blood could not be obtained for one patient. In the meperidine group, neither umbilical arterial nor venous blood could be sampled for one patient for technical reasons.

Maternal characteristics, except parity, were comparable in the two groups (Table 1). The meperidine group had greater parity (P=0.014). All patients had adequate sensory block for surgery. Block height for the saline group ranged from C5 to T6 and from C4 to T5 for the meperidine group (Table 2). The median level of block was T1–T2 for both groups. The times from spinal injection to incision, spinal injection to delivery and uterine incision to delivery and the duration of surgery were similar between groups. Neonatal outcome was also similar between groups.

Eleven patients in the meperidine group had nausea and vomiting after correction of hypotension compared with three patients in the saline group (P=0.02; Table 3). Ephedrine requirement was similar between groups. No patient had pruritus or respiratory depression. Two patients in the saline group complained of discomfort during surgery, one of whom received alfentanil 200 µg i.v.. There were no complaints of intraoperative discomfort from patients in the meperidine group.

Mean duration of sensory block was greater in the meperidine group (129 (SD 24.0) min) compared with the saline group (113 (21.5) min; P=0.028). The mean duration of effective analgesia was greater in the meperidine group (234 (95% confidence interval 200–269) min) compared with the saline group (125 (111–138) min, $P<0.001$) (Fig. 1). Two hours after intrathecal injection, mean cumulative morphine consumption was greater in the saline group (0.8 (1.3) min) compared with the meperidine group (0.1 (0.2) min; P=0.013) (Table 4). At 6 h, mean cumulative morphine consumption was greater in the saline group (12.8 (6.0) min) compared with the meperidine group (6.6 (5.2) min; P=0.002). At 24 h, mean cumulative morphine consumption was similar between groups. During the epoch between 6 and 24 h, mean morphine consumption was greater in the meperidine group (32.1 (9.6) mg) compared with the saline group (22.5 (11.0) mg; P=0.008).

Postoperative side-effects of nausea, pruritus and drowsiness were mild and similar between groups. No patient in either group showed respiratory depression whilst using PCA or had signs of residual neurological effects 24 h later.

Discussion

We found that the addition of meperidine to intrathecal hyperbaric bupivacaine increased the duration of effective analgesia after elective Caesarean section compared with placebo. Although postoperative pain relief after Caesarean section with intrathecal meperidine and bupivacaine mixtures has been described previously, there was no comparison with a placebo group.[14] Studies of the addition of other opioids to intrathecal bupivacaine in which postoperative PCA was used showed that fentanyl 15 µg increased the mean duration of effective analgesia from 124 to 184 min[15]

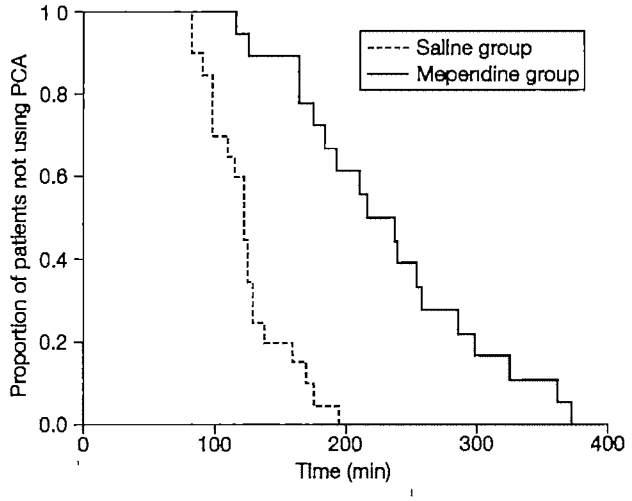

Fig 1 Survival curves showing duration of effective analgesia (time from intrathecal injection to first PCA demand). The broken line depicts the saline group (mean duration of analgesia 125 min (95% confidence interval 111–138)) and the solid line depicts the meperidine group (234.1 (200–269) min; $P<0.001$).

and diamorphine 0.25 mg increased the duration of effective analgesia up to a mean of 201 min compared with 75 min for placebo.[16] To our knowledge, data assessing postoperative analgesia using PCA have not been reported for intrathecal sufentanil and bupivacaine mixtures.

The assessment of morphine consumption by PCA provides an objective measurement of postoperative pain and analgesic requirements.[6 7 15–18] It has the advantages of accurate, objective assessment of the timing and titration of analgesic use by patients with a minimum of external interference. Additionally, data from different studies can be compared using the same end-points. We did not assess visual analogue scale pain scores in this study. Although inclusion of pain scores may have added further information on the patients' postoperative analgesic requirement, care must be taken in the interpretation of such data as pain scores are likely to be reduced by concurrent consumption of analgesics via PCA, resulting in convergence of data.

Although we found that the meperidine group had prolonged analgesia and less morphine consumption than the saline group up to 6 h after injection, conversely, during the period from 6 to 24 h, morphine consumption was greater in the meperidine group compared with the saline group, thus causing the overall cumulative morphine consumption at 24 h to be similar. The explanation of this finding is unclear. It is possible that the high local concentration of opioid introduced intrathecally may have induced either acute spinal opioid tolerance[19] or hyperalgesia.

Nausea and vomiting are troublesome side-effects encountered during spinal anaesthesia for Caesarean section. Possible aetiologies include hypotension and peritoneal manipulations that stimulate vagal afferents. With intrathecal opioids, a direct opioid effect can also be a factor. We found an increased incidence of intraoperative nausea or vomiting in the meperidine group compared with the saline group after correction of hypotension. Previously, intrathecal meperidine 10 mg alone was found to be associated with more nausea or vomiting than fentanyl and sufentanil when used in continuous spinal analgesia for labour analgesia.[20] Larger doses of intrathecal meperidine used as the sole agent for spinal anaesthesia in Caesarean section have also been associated with nausea or vomiting.[9–11] These studies indicate that intrathecal meperidine, in doses as low as 10 mg, can increase nausea or vomiting. In contrast, a review of randomized controlled trials of intrathecal opioids in spinal anaesthesia for Caesarean section concluded that nausea or vomiting does not increase with fentanyl or sufentanil, although it does with morphine.[4] Recently, intrathecal fentanyl has been shown to be more effective than i.v. ondansetron in preventing intraoperative nausea or vomiting during spinal anaesthesia for Caesarean section.[21] These data suggest that fentanyl may be a better choice than meperidine as an adjunctive intrathecal agent during spinal anaesthesia for Caesarean section when nausea and vomiting are considered.

Table 4 Cumulative morphine consumption by patient-controlled analgesia (mean (SD))

Time after intrathecal injection (h)	Saline group (*n*=19)	Meperidine group (*n*=18)	*P*
2	0.8 (1.3)	0.1 (0.2)	0.013
6	12.8 (6.0)	6.6 (5.2)	0.002
24	35.3 (11.2)	38.7 (10.6)	0.35

Lipid-soluble opioids have been shown to decrease discomfort from intraoperative peritoneal manipulations when combined with intrathecal bupivacaine,[1 5 15 16] though the value of this has been questioned.[4] In our study, the incidence of intraoperative discomfort or pain during surgery was very small in both groups and there was thus insufficient statistical power to reveal a difference. Comparisons between studies should be made with care because differences in surgical technique may affect the amount of additional intraoperative analgesia required.

Pruritus has been associated with intrathecal fentanyl,[1 2] sufentanil,[3 22–24] diamorphine[16] and morphine.[5–7 25 26] In our study, no patient complained of pruritus during the operation and only a small number had pruritus afterwards. In studies in which the dose of intrathecal meperidine was 50 mg or greater, the incidence of pruritus ranged from 10.7 to 32%.[9–11] A dose-dependence study of intrathecal meperidine would demonstrate whether pruritus occurs in a dose-dependent fashion but would probably incur an undesirably high incidence of nausea and vomiting.

We found that regression of spinal anaesthesia was prolonged with patients who received intrathecal meperidine. This feature is consistent with other studies of co-administration of bupivacaine with lipid soluble opioids.[1–3 15] Intrathecal opioids potentiate the action of intrathecal local anaesthetics and the inherent local anaesthetic properties of meperidine may have contributed in our study.

Our patients had no neurological symptoms 24 h after operation. There are no reports in the literature to suggest that intrathecal meperidine is associated with long-term neurological dysfunction.[8] Respiratory depression has been reported with intrathecal meperidine but typically at doses above 50 mg or with concurrent use of other sedatives.[8 27] Unlike morphine, meperidine has not been reported to be associated with delayed respiratory depression. No patient in our study had respiratory depression either during or after the operation.

In summary, the addition of intrathecal meperidine 10 mg to hyperbaric bupivacaine prolonged analgesia after elective Caesarean section compared with placebo, although the duration of effective analgesia was limited to approximately 4 h. Meperidine has the advantages of being widely available and inexpensive. However, an important limitation of its use is increased intraoperative nausea and vomiting. Further studies, with prophylactic antiemetics or using smaller doses of meperidine, are required to determine whether nausea and vomiting can be reduced whilst maintaining an increased duration of postoperative analgesia.

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Abdominal pressure during laparoscopy: effects of fentanyl[†]

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Background. In patients breathing spontaneously during anaesthesia, expiration is active and opioids enhance this effect. The mechanical consequences are not well characterized.

Methods. We studied 14 patients undergoing laparoscopy for minor gynaecological procedures, anaesthetized with isoflurane in nitrous oxide, and breathing spontaneously through a laryngeal mask airway. We made direct recordings of intra-abdominal pressure and respiratory flow before and after giving fentanyl 25 µg i.v.

Results. Satisfactory records were obtained in 11 patients. Before fentanyl, the abdominal pressure changes were small and had an inconsistent pattern, increasing in inspiration in seven patients and during expiration in five. After fentanyl, an increase in pressure during inspiration was seen in only two patients, and the intra-abdominal pressure during expiration was increased. The mean value of maximum abdominal pressure (which always occurred during expiration) increased from 17 (SD 5) cm H_2O before to 25 (9) cm H_2O after fentanyl ($P<0.01$).

Conclusions. Direct measurements support previous findings that opioids stimulate active phasic expiratory activity and can cause large increases in abdominal pressure.

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Keywords: analgesics, opioid, fentanyl; muscles, respiratory

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Patients are often anaesthetized for laparoscopic gynaecological procedures breathing spontaneously with a laryngeal mask airway (LMA[‡]).[1] In these circumstances, opioids have to be given in small doses to avoid excessive respiratory depression. We noted that even when a small dose of fentanyl was given, abdominal pressure increased and the high-pressure alarm on the carbon dioxide insufflator was often activated. Previous studies have shown that large doses of fentanyl frequently cause rigidity,[2] but generally reported truncal rigidity, rather than a specific effect on abdominal muscles. Morphine in large doses can increase abdominal muscle activity,[3] but the actual dose required to cause this phenomenon and the resultant mechanical effects were not evident. We have measured the effects of a small dose of fentanyl (25 µg) on intra-abdominal pressure.

Materials and methods

After ethics committee approval, we obtained written informed consent from 14 women, ASA I or II, about to have gynaecological laparoscopy as a day-case procedure. We noted their age, height and weight. A venous cannula was placed in the dorsum of the hand and anaesthesia was induced with up to 50 mg of propofol, followed by inhalation of sevoflurane in nitrous oxide and oxygen. No other drugs were administered at induction and no patient received premedication. After an adequate depth of anaesthesia was attained, an LMA was inserted. Anaesthesia was maintained with isoflurane in nitrous oxide and oxygen, breathed from a circle system with a carbon dioxide absorber. At the end of the surgical procedure, all ports and instruments were left in place and the intra-abdominal pressure was measured from a connection to the carbon dioxide insufflator tubing using a differential pressure transducer (Gaeltec TC50, Gaeltec, Dunvegan, Isle of Skye, UK). The insufflator was switched off so that the tubing acted as a passive connection to the abdominal cavity. Gas was not vented from the abdomen until the study

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Table 1 Patient characteristics and respiratory measurements before and after giving fentanyl

Patient	Age	Height (cm)	Weight (kg)	$F\text{I}_{\text{O}_2}$		$P\text{E}'_{\text{CO}_2}$		% N_2O		$F\text{E}'_{\text{iso}}$		Respiratory frequency	
				Before	After	Before	After	Before	After	Before	After	Before	After
1	44	165	54	0.32	0.31	5.2	5.2	65	66	1.2	1.2	34	29
2	42	163	68	0.31	0.32	5.6	6.5	65	64	1.3	1.2	38	29
3	40	165	60	0.37	0.37	6.3	6.3	51	52	1.7	1.5	21	14
4	37	173	66	0.33	0.3	5.7	7.2	61	62	1.3	1.2	38	22
5	37	155	59	0.32	0.33	5.4	5.8	63	64	0.8	0.8	26	16
6	35	159	73	0.3	0.29	4.6	5	64	65	0.9	0.9	39	32
7	33	163	60	0.39	0.37	6.5	6.8	49	52	1.5	1.4	22	14
8	31	168	69	0.33	0.34	6.2	6.5	63	63	1.1	1	23	14
9	28	163	63	0.32	0.31	4.3	5.2	64	66	0.8	0.8	36	28
10	25	170	76	0.31	0.31	5	5.5	65	66	1.1	1	36	27
11	18	172	64	0.22	0.19	5.2	5.5	64	69	1.7	1.3	43	29
Mean	33	165	64	0.32	0.31	5.45	5.95	61	62	1.21	1.11	32	23
SD	8	5	6	0.04	0.05	0.7	0.74	6	6	0.33	0.25	8	7
Minimum	18	155	60	0.3	0.19	5.03	5	55	52	1.12	0.76	29	14
Maximum	44	173	60	0.29	0.37	4.92	7.2	55	69	1.07	1.5	30	32

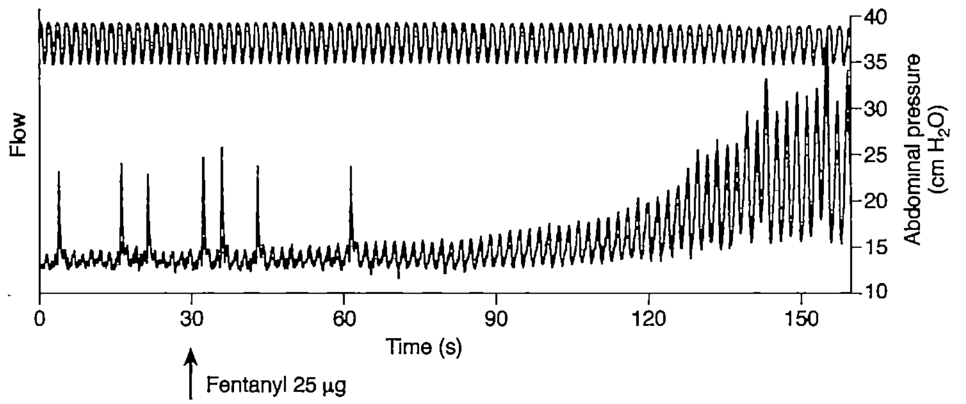

Fig 1 Time course of change in respiratory flow (upper trace) and abdominal pressure (lower trace) after fentanyl in a representative patient. The spikes of pressure on the trace represent artifact caused by movement by the surgeons

recordings were completed. The pressure signal was digitized by a data acquisition system (1401 interface and Spike 2 software, CED, Cambridge, UK) and Spike 2 software. We also recorded a signal indicating respiratory flow by measuring the pressure drop across a second breathing filter at the patient connection using a differential pressure transducer (Furness FC 10, Furness Controls Ltd, Bexhill, East Sussex, UK). This signal allowed the changes in intra-abdominal pressure to be related to the phase of respiration. The respiratory rate, inspired concentration of oxygen, and end-tidal concentrations of carbon dioxide, nitrous oxide and isoflurane were recorded from the digital display of a Capnomac monitor, which sampled continuously at the patient connection.

When the breathing pattern and inspired and expired gas compositions were stable, abdominal pressure and respiratory flow waveforms were recorded for 30 s. Fentanyl, 25 µg in 5 ml normal saline, was given rapidly intravenously, followed by 5 ml normal saline. Pressure and flow were recorded for a further 2 min. At the end of this time measurements were stopped, abdominal gas was released, the cannulae were removed and clinical management was continued. We took readings of inspired and end-tidal values from the gas analyser just before and 2 min after administration of fentanyl. Recordings were also made in two patients in whom only the saline flush was administered.

Pressure and flow signals were converted into text files and analysed using a spreadsheet program on a personal computer. The pressure transducer was calibrated using a water manometer.

We analysed three complete respiratory cycles, immediately before and 100 s after giving fentanyl. We displayed these data graphically and measured the following values in each cycle: the minimum intra-abdominal pressure during inspiration; the intra-abdominal pressure at onset of expiration; the maximum intra-abdominal pressure during expiration; and the intra-abdominal pressure at the end of expiration. We also measured the time from the start of each respiratory cycle to each chosen value. We took means of

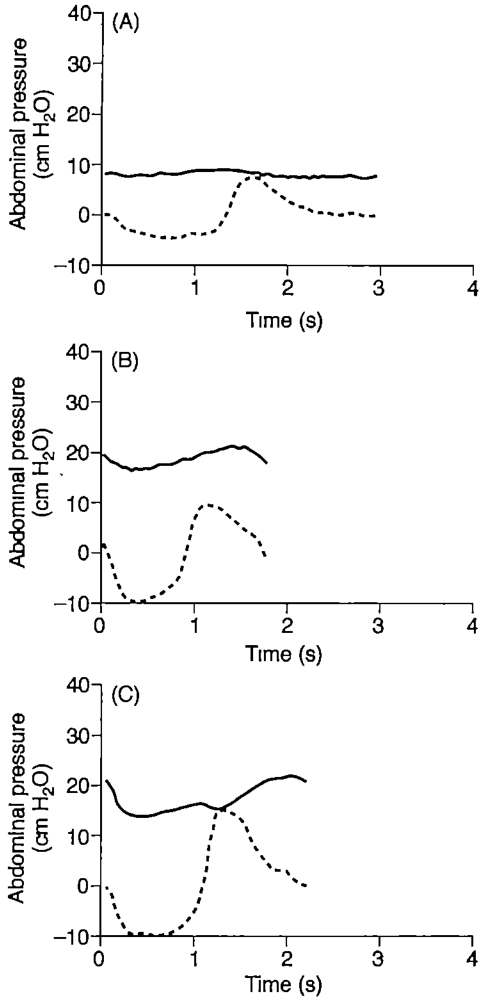

Fig 2 Examples of different pressure waveforms. Broken line: respiratory flow (inspiration downward deflection) (A) A small increase during inspiration, (B) increase during expiration; (C) increases during both inspiration and expiration

the measurements from the three cycles and constructed an average respiratory pressure cycle for each patient, before and after fentanyl.

Statistics

Group results are expressed as mean and SD and data were analysed by paired t test (Minitab v 12.1, Minitab Ltd, Coventry). Statistical significance was assumed if $P<0.05$.

Results

We recruited 14 women, and present data from 11. Three patients were excluded, two because of gas leakage at port sites causing loss of the pneumoperitoneum during recording, and one because the exact time of fentanyl administration was not recorded. For the remaining 11 patients, mean age was 34 (range 18–45 yr), mean weight (SD) was 65 (5) kg and mean height 165 (6) cm. These and other characteristics are shown in Table 1. As expected, after giving an opioid, PE'_{CO_2} increased from 5.4 (0.7) to 6.0 (0.7) kPa and respiratory rate decreased from 32 (8) to 23 (7) bpm. A record of pressure and flow from a typical patient is shown in Figure 1, demonstrating a progressive change in breathing pattern with prolongation of expiration, and a simultaneous, marked increase in abdominal pressure changes during expiration.

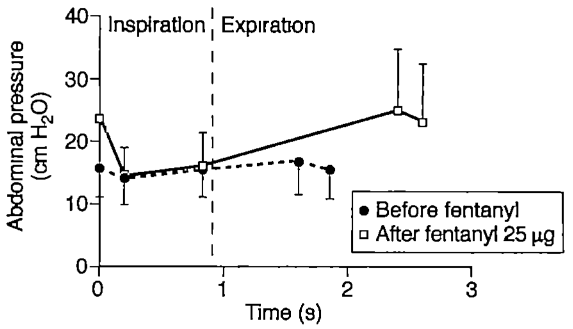

Fig 3 Mean (SD) pressure and time during the respiratory cycle in all patients studied. The end of inspiration is marked by the vertical broken line. Broken line: before fentanyl, solid line: 100 s after fentanyl

Before fentanyl was given, we noted three patterns of abdominal pressure change within the respiratory cycle: (i) pressure increase during inspiration only (six patients); (ii) pressure increase during expiration (four patients); (iii) biphasic changes in pressure, increasing at the end of inspiration and again towards the end of expiration. This pattern was seen in only one subject before giving fentanyl, but was noted after fentanyl in two patients. Examples are given in Figure 2.

After fentanyl, in all but one patient (Patient 3), a large increase in intra-abdominal pressure during expiration was noted. A small increase during inspiration was seen in two other patients, as noted above. Minimum abdominal pressure (which occurred during inspiration) increased from 13 (4) to14 (4) cm H_2O after fentanyl. Maximum abdominal pressure (which occurred during expiration) increased from 17 (5) to 25 (9) cm H_2O after fentanyl and the duration of expiration was increased from 1.1 to 1.8 s (both $P<0.01$). Figure 3 summarizes these changes for the whole group, showing the mean pressures and times during an average respiratory cycle before and after fentanyl. The pressure changes over the period of expiration increased significantly after fentanyl ($P<0.01$).

Discussion

In normal quiet breathing in the conscious subject, inspiration is an active process involving contraction and descent of the diaphragm. The pressure in the abdomen increases. If the subject is upright, the abdominal muscles are more active than in the supine position, and the increase of pressure in the abdomen associated with contraction of the diaphragm is greater than when the subject is supine.[4] Expiration is usually passive, and as the diaphragm relaxes, intra-abdominal pressure decreases. However, during anaesthesia with spontaneous respiration, activity of the abdominal muscles has been recorded during expiration,[5 6] and opioids enhance this activity.[3] Thus abdominal pressure rises in expiration.[5] In normal conscious subjects, little or no activity is found in the recti or external oblique muscles, but activity is usually present in the transversus abdominis and internal oblique muscles, indicating that expiration is always active to some extent.[7] A progressive increase in abdominal muscle action during pentobarbital anaesthesia has been reported in dogs.[8]

In some of the patients we studied, abdominal pressure increased during inspiration, caused by contraction of the diaphragm. In normal conscious subjects, this is the major influence on abdominal pressure. However, in our subjects this pressure change was small, and in some patients no increase in pressure during inspiration was detected, suggesting that either the diaphragm was contracting poorly or that this pressure change was concealed by the actions of other muscles. For example, relaxation of the abdominal muscles or, less likely, inspiratory activity of the rib-cage muscles could reduce the increase in abdominal pressure during inspiration and conceal any pressure change generated by contraction of the diaphragm.

Pressure changes consistent with some expiratory activity of the abdominal muscles were noted before opioid administration but these changes increased markedly and consistently after fentanyl. The close temporal relationship of these changes to the injection, and the characteristics of fentanyl, make other causes very unlikely. There were no changes in breathing pattern, gas measurements, or pressure after saline administration. We made measurements of the effects after 100 s because this would reliably give three breaths to analyse before the recording stopped at 120 s. We did not have ethical permission to prolong the recording further, and it is possible that the pressure changes were not maximal when we made our measurements. However, because ventilation is reduced, other confounding factors such as carbon dioxide tension, anaesthetic depth, and perhaps cerebral blood flow, will be changing too. Early measurements allow these factors to have less impact, and interpretation of changes noted after prolonged observations would have to be limited. Other studies have shown that the effects of fentanyl in the conscious subject take considerably longer to cause rigidity,[9] and some even suggest that loss of consciousness may be a necessary condition for the feature to develop.[10] Such observations are consistent with the cerebral kinetics of fentanyl,[11] but animal studies suggest that the rigidity may be mediated by brainstem structures and it is evident that the respiratory effects of fentanyl are equally prompt.

Although these effects of opioids have been noted before, our study shows that a modest dose can cause a considerable increase in abdominal pressure change during expiration, to well above the limits usually set for gas insufflation during laparoscopy. However, the pressures generated by maximum expulsive efforts can be at least 10 times the values we noted.[12] Distension of the abdomen by gas insufflation during laparoscopy would increase the length of the abdominal muscle fibres and might augment the tension the fibres could generate and the pressure changes produced. However, animal experiments suggest that the abdominal muscles, in contrast to the diaphragm, normally work over a limited range of fibre length.[13]

The effects of opioids on the abdominal muscles may be increased during anaesthesia. In healthy conscious volunteers, morphine 2 mg kg^{-1}, caused abdominal muscle activity in expiration and this activity was greatly increased by 70% nitrous oxide, which caused ‘board-like’ rigidity and prevented mechanical ventilation.[3] Abdominal muscle activity of this degree is potentially harmful, reducing the lung volume at end expiration, which could impair gas exchange by causing airway closure.[14] During laparoscopy, abdominal muscle contraction will reduce the volume of gas that can be introduced before the pressure limit of the insufflator is reached and this could impair surgical access. During pelvic floor surgery, increased venous pressure caused by increased abdominal pressure may cause excessive bleeding. Abdominal muscle action can cause abnormal patterns of respiratory movement, which could be difficult for the inexperienced anaesthetist to distinguish from movements seen when airway obstruction is present, and lead to misdiagnosis and mismanagement of the airway.

There are several agents that could potentially reduce this effect. Although μ opioid effects are responsible for increased muscle tone, the effects are reduced by δ_1 or κ_1 opioid agonists.[15] Opioids increase muscle activity by action at several central sites, including the peri-aqueductal grey matter and the locus coeruleus. Lesions in the latter site reduce the ability of opioids to increase muscle tone[16] and it is possible that other agents that act at this site, such as α_2 adrenergic agonists, could modulate this process. The control of muscle tone from the locus coeruleus is by α_1-adrenergic and glutaminergic pathways, probably arranged in series.[17] The α_1 antagonist prazosin antagonizes the central effects of opioids whereas the spinal α_2 blocker yohimbine does not.[18]

In summary, respiration is active in both expiration and inspiration but in the normal conscious subject expiratory activity in the abdominal muscles is small. Both anaesthesia and opioids can increase this activity. Even a small dose of opioid during anaesthesia increases abdominal pressure during expiration. In our patients, the expiratory pressure changes dominated the pressure waveform, suggesting a radical change in the mechanics of breathing in the anaesthetized patient given an opioid. During anaesthesia with spontaneous breathing, anaesthetists should be aware of the marked changes in abdominal pressure that can be brought about by even small doses of fentanyl.

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Phonomyography of the corrugator supercilii muscle: signal characteristics, best recording site and comparison with acceleromyography

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Background. This study investigated the acoustic signal characteristics and best recording site of phonomyography at the corrugator supercilii muscle and compared phonomyography with acceleromyography.

Methods. In 12 patients (group I), after induction of anaesthesia and insertion of a laryngeal mask, a microphone (frequency range 2.5 Hz to 10 kHz) was placed on six different areas on the forehead and the peak-to-peak response after single-twitch stimulation of the facial nerve was measured. The microphone was placed where the response was largest and mivacurium 0.2 mg kg $^{-1}$ was administered. Fast Fourier transformation was applied to all signals to determine peak frequencies and the power–frequency relationship at different stages of neuromuscular block. In an additional 15 patients (group II), the same microphone and an acceleromyographic probe were placed above the middle portion of the left and right eyebrows respectively. Onset and offset of neuromuscular block were determined after mivacurium 0.2 mg kg $^{-1}$.

Results. In all seven women and all five men in group I, the best response was obtained just above the middle portion of the eyebrow. Peak frequency was 4.1 (SD 0.9) Hz without neuromuscular block and did not change significantly during onset and offset of neuromuscular block. Ninety per cent of the total signal power was below 40 Hz. In group II, mean onset time and maximum effect measured were 104 (20) s and 76 (10)% respectively using acceleromyography and 134 (30) s and 92 (4)% using phonomyography ($P<0.04$). Mean time to reach 25, 75 and 90% of control was 9.5 (2.8), 14 (5.1) and 15.1 (5.3) min respectively using acceleromyography and 6.9 (2.8), 12.5 (5.9) and 13.6 (4.9) min using phonomyography ($P<0.04$). Bland-Altman testing revealed significant bias (precision) for onset time, maximum effect and time to reach 25% of control (acceleromyography minus phonomyography) at –30 (38) s, –16 (11)% and 2.6 (2.8) min respectively.

Conclusions. Phonomyography can be used to determine neuromuscular block at the corrugator supercilii muscle. In comparison with acceleromyography, phonomyography tends to measure a longer onset with more pronounced maximum effect and shorter recovery of neuromuscular block.

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The contraction of skeletal muscles generates intrinsic low-frequency sounds,[1] which can be used to monitor neuromuscular block.[2 3] The corrugator supercilii muscle is a small muscle under the medial portion of the eyebrow,[4]

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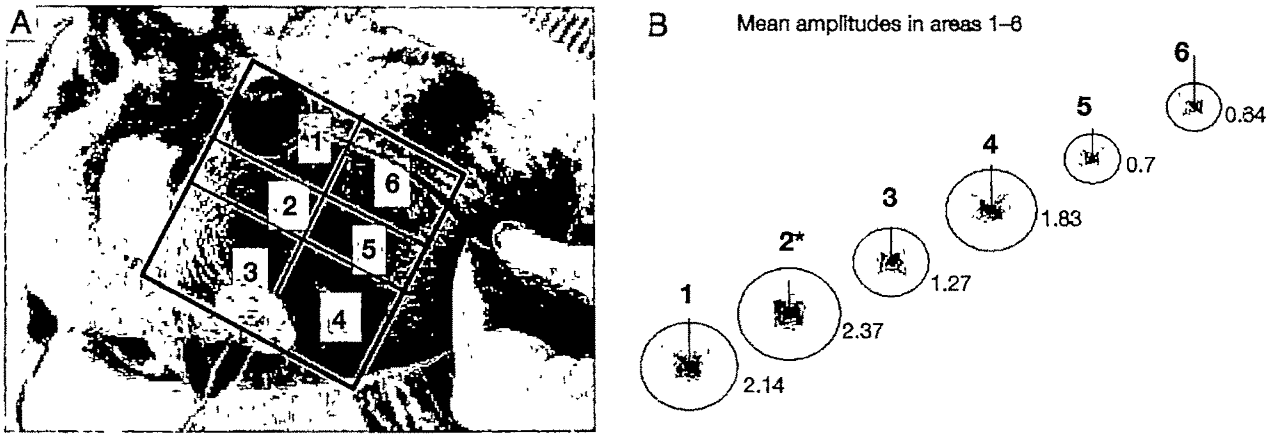

Fig 1 (A) Mapping the forehead for optimal signal detection The forehead was divided into six areas (numbered 1–6) Recording of supramaximal signals was started in area 1 and ended in area 6 Train-of-four signals and single-twitch responses were recorded and measured in all areas Monitoring the neuromuscular blockade was then commenced in area 2, which provided the maximal responses in all patients (B) Mean amplitudes and standard deviations of supramaximal responses in areas 1–6. Diameters of circles reflect mean amplitude; bars indicate the standard deviation. $^*P<0.05$ *vs* amplitude in areas 1 and 3–6.

where onset and offset of neuromuscular block are shorter and less intense than in the adductor pollicis muscle. The time course of neuromuscular block is similar at the corrugator supercilii muscle and at the larynx.[5 6]

This study was designed to establish the optimal site for acoustic signal recording of the corrugator supercilii muscle and to analyse the signal using Fourier transformation. Phonomyography was then used to determine onset and offset of neuromuscular block at the corrugator supercilii muscle after mivacurium and to compare it with acceleromyography.

Patients and methods

We obtained institutional ethics committee approval and informed consent from all patients. Twenty-seven patients (ASA physical status 1–3) undergoing elective general surgery were included. Pregnant women, patients with neuromuscular, hepatic or renal disease and patients receiving medications known to interact with neuromuscular blocking drugs were excluded. Anaesthesia was induced with propofol 1–2.5 mg kg^{-1} and remifentanil 0.1–0.5 μg kg^{-1} min^{-1}. After loss of consciousness, a laryngeal mask was inserted. Anaesthesia was maintained with 1–1.5 minimum alveolar concentration (MAC) sevoflurane in a breathing gas mixture of 30% oxygen in air, and remifentanil 0.05–0.25 μg kg^{-1} min^{-1}. Minute ventilation was set to maintain $P\mathrm{E}'_{\mathrm{CO_2}}$ at 3.5–4.5 kPa.

Phonomyography

Stimulation of the motor branches of the facial nerve supplying the corrugator supercilii muscle was performed using two Ag/AgCl electrodes (diameter 3.5 cm) (Safelead; Grass Instruments, Astro-Med, West Warwick, USA) at both temporal areas in group I (*n*=12) and the unilateral temporal area in group II (*n*=15). A constant-current stimulator (Innervator; Fisher and Paykel Healthcare, Auckland, New Zealand) generated single-twitch square pulses of 0.2 ms with a current intensity of 20 mA (single twitch 0.1 Hz, train-of-four stimulation once every minute). A small microphone (diameter 1.6 cm; frequency response 2.5 Hz to 5 kHz, signal output 20–40 mV into 1 MΩ) (Model 1010, Grass Instruments, Astro-Med, Rhode Island, USA) was taped above the eyebrow for recording the evoked responses of the corrugator supercilii muscle. The microphone signal was amplified and bandpass-filtered between 0.5 and 1000 Hz using an AC/DC amplifier (Model 7P122, Grass Instruments, Astra-Med).

Acceleromyography

In 15 patients (group II), two Ag/AgCl electrodes were placed on the right temporal area to stimulate the motor branches of the right facial nerve supplying the corrugator supercilii muscle. They were connected to a TOF watch SX (Organon Instruments, Boxtel, Netherlands) for single-twitch (0.1 Hz) and train-of-four stimulation (once every minute). The acceleromyographic probe of the TOF watch SX was taped above the right medial eyebrow as the microphone on the left side (Fig. 1). Maximum sensitivity of the TOF watch SX was set for all patients.

Part I

Mapping and Fourier analysis

Twelve patients were included in the first part of the study. The forehead was divided into six areas (Fig. 1A). After stimulation of the facial nerve with single-twitch impulses at 20 mA and 0.1 Hz, the microphone was placed consecutively at areas 1–6, starting medially at area 1 and ending at area 6, more distant to the eyebrow. This mapping was used to determine the site of maximal evoked responses of the corrugator supercilii muscle. Signals were recorded and the microphone was placed at the area where the maximal response was found. After supramaximal stimulation for at least 3 min (20 mA, single-twitch 0.2 ms, 0.1 Hz; train-of-four stimulation every minute), mivacurium 0.2 mg kg^{-1} was injected within 5 s in a fast-flowing infusion of Ringer's lactate. Phonomyographic monitoring was maintained until train-of-four responses reached a T4/T1 ratio of at least 1 or showed no increase for 15 min.

Signal processing and analysis

The signals were sampled continuously at 1000 Hz using the Polyview software package (Astra-Med), digitized, and stored on a portable microcomputer. The single-twitch phonomyography signal was measured peak-to-peak and processed using Fourier transformation to determine the peak frequency and the power–frequency relationship of the signal at control stimulation and (at the best recording site) throughout the period of neuromuscular block. Fast Fourier analysis was used to calculate the power under various frequency cut-offs relative to the total power of the frequency domain under 500 Hz. The cut-offs were 10, 20, 30, 40, 50, 100, 200, 300 and 400 Hz.

Statistical analysis

Patient data and all pharmacodynamic variables are presented as the mean and standard deviation. One-way analysis of variance (ANOVA) was used to define significant differences in signal amplitude among the six areas of mapping. One-way analysis of variance (ANOVA) was also used to determine significant differences between the mean peak frequencies in relation to onset and offset of neuromuscular block, when the first decrease in the control amplitude was detected (lag time), at 50% block (onset 50), maximum blockade and 25, 75 and 90% recovery. $P<0.05$ was considered to show a statistically significant difference. Statistical analysis was performed using a commercial software package (Statview; SAA Institute, Cary, NC, USA).

Part II

Comparison between acceleromyography and phonomyography

Fifteen patients were included in this part of the study. After induction of anaesthesia, insertion of the laryngeal mask and application of the acceleromyography and phonomyography monitoring devices at the optimal recording site determined in part I, supramaximal stimulation (20 mA, single-twitch 0.2 ms, 0.1 Hz; train-of-four stimulation every minute) was initiated and after at least 3 min mivacurium 0.2 mg kg^{-1} was injected within 5 s in a fast-flowing infusion of Ringer's lactate solution. Onset and recovery of neuromuscular block were determined by phonomyography and acceleromyography. Monitoring was maintained until train-of-four responses reached a T4/T1 ratio of at least 1 or showed no increase for 15 min.

Statistical analysis

Group size was chosen to achieve a power of more than 0.9, based on calculation of an expected difference in the mean of onset time of 20% and a standard deviation of 20% of the mean. Patient data and all pharmacodynamic variables are presented as mean and standard deviation. Pharmacodynamic data were compared between phonomyography and acceleromyography using the paired *t*-test; $P<0.05$ was considered to show a statistically significant difference. The extent to which the two methods were in agreement was tested by the method of Bland-Altman. $P<0.05$ was regarded as showing a statistically significant difference. Statistical analysis was performed with Statview.

Results

Part I

The mean age of the seven women and five men was 53 (38–78) yr and the mean weight was 71 (19) kg.

Mapping

In all patients, the maximum evoked response of the corrugator supercilii muscle was obtained in area 2 (Fig. 1B), with a mean maximum amplitude of 2.37 (SD 0.67) mV at a mean peak frequency of 4.13 (0.9) Hz. All other areas provided signals which were significantly smaller ($P<0.01$) but had the same biphasic shape and mean peak frequencies. In all patients, a signal from the contralateral corrugator supercilii muscle could be detected at a mean amplitude of 0.8 (0.6) mV; the shape of the acoustic signal was inverted and its amplitude was 34% of the signal of the ipsilateral corrugator supercilii.

Fourier transformation

The peak frequencies were in the ranges of 2.5 and 5 Hz. Analysis in the frequency domain showed that signal recording up to 40 Hz detected 90% of the total signal power. In three of 12 patients, the microphone recorded acoustic signals at the same frequency as the patient's pulse at a mean amplitude of 0.1 (0.02) mV and a peak frequency of 3.4 (0.3) Hz, as a monophasic signal. Train-of-four-evoked stimulation phonomyographic signals showed an equal height for all four twitches at a mean duration of 2.03 (0.06) s before injection of mivacurium followed by typical fade.

After complete neuromuscular block, recovery to a T4/T1 ratio of ≤1 and a height of T1 between 80–120% of control was reached in all patients.

Part II

The mean age of eight women and seven men was 51 (35–79) yr and mean weight was 67 (13) kg. In seven of the

15 patients, time to reach 25% of control twitch height could not be determined by acceleromyography because the maximum effect was less than 75%. Table 1 shows the values for onset and offset of neuromuscular block measured by acceleromyography and phonomyography. There was no significant difference between lag time and the time to reach a 50% decrease in control twitch height between the two methods. The onset time was significantly longer, the maximum effect more pronounced and recovery from neuromuscular block faster when determined by phonomyography in comparison with acceleromyography. Bland-Altman calculations showed significant systematic bias and wide limits of agreements for all pharmacodynamic variables (Fig. 2). Bias, precision and limits of agreement for all variables are presented in Table 2.

Discussion

Phonomyography is a quantitative and sensitive monitor of neuromuscular block of the corrugator supercilii muscle. Low-frequency signals can be obtained and clearly distinguished after single-twitch or train-of-four stimulation, and the signal frequency is stable, reproducible and independent of block. Mapping the forehead revealed that the optimal area for recording the acoustic responses of the corrugator supercilii muscle lies not directly over the muscle but more laterally, just above the eyebrow (area 2 in Fig. 1). Peak frequencies were within a narrow range between 2.5 and 5 Hz and did not change significantly throughout the study period; 90% of the signal power can be recorded if the upper frequency of recording is limited to 40 Hz.

The pharmacodynamic data determined using acceleromyography and phonomyography cannot be used interchangeably and differed most significantly in the maximum effect, onset time and time to reach 25% recovery from block (acceleromyography *vs* phonomyography: 76 *vs* 92%, 104 *vs* 134 s and 9.5 *vs* 6.9 min). With acceleromyography, one obtains a shorter onset time (bias –30 s), with less maximum effect (bias –16%), and a longer offset of neuromuscular block (bias for time to reach 25% of control, +2.5 min).

The location of the best recording areas reflects muscle anatomy. It follows the contraction line of vertical frowning from the medial aspect just above the eyebrow (area 1) to the lateral distal site (area 4). The sensitivity of the microphone is such that even in the area where the signal

Table 1 Pharmacodynamic data of 15 patients after mivacurium 0.2 mg kg^{-1} Lag time is the time to reach the first decrease in control twitch height, onset 50 is the time to reach a 50% decrease in control twitch height, onset time is the time to reach maximum effect; maximum effect is the maximum depression of control twitch height, T 25%, T 75%, T 90% are the times to reach 25%, 75% and 90% recovery of control value respectively Data are mean (SD)

	Acceleromyography	Phonomyography	*P*
Lag time (s)	29 (12)	36 (35)	0.21
Onset 50 (s)	80 (13)	74 (34)	0.26
Onset time (s)	104 (20)	134 (30)	0.005
T 25% (min)	9.5 (2.8)	6.9 (2.8)	0.02
T 75% (min)	14 (5.1)	12.5 (5.9)	0.04
T 90% (min)	15.1 (5.3)	13.6 (4.9)	0.02
Maximum effect (%)	76 (10)	92 (4)	<0.001

Table 2 Bias, precision and limits of agreement between acceleromyography and phonomyography Bias is the mean difference acceleromyography minus phonomyography, precision is the standard deviation of bias, and limits of agreement is bias ± standard deviation of bias

	Bias±precision	Limits of agreement
Lag time (s)	–7±33	–70 to + 59
Onset 50 (s)	6±36	–66 to + 78
Onset time (s)	–30±38	–106 to + 46
T 25% (min)	2.6±2.8	–3 to + 8.2
T 75% (min)	1.5±2.8	–4.1 to + 7.1
T 90% (min)	2.5±3.5	–4.5 to + 9.5
Maximum effect (%)	–16±11	–38 to + 8

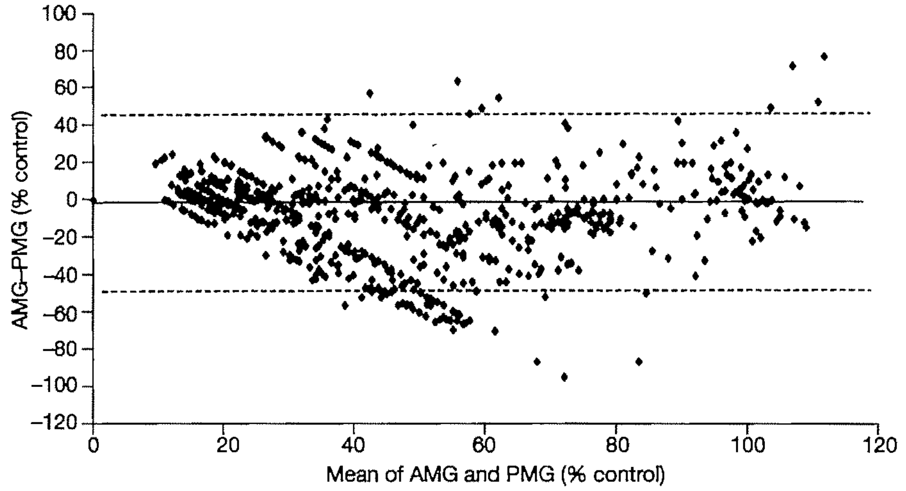

Fig 2 Mean of acceleromyographic and phonomyographic values (percentage of control).

response was weakest (area 5), 27% of the maximal signal height could still be recorded. Even acoustic signals from the opposite corrugator supercilii muscle could be recorded, and these reached 34% of the maximal signal height of the same side. It could, however, be easily identified in all patients because of the opposite direction of the signal.

Barry and collegues[7] have shown that high-pass filtering of the signals at 30 Hz effectively removes artefacts due to motion. According to our frequency domain analysis, however, filtering the signals above 30 Hz would mean that 16% of the signal power would be lost.

The peak frequencies measured for the corrugator supercilii muscle differ substantially from the peak frequencies of other muscles[7] and from signals derived from either voluntary contraction or tetanic stimulation,[8] which are usually in the range of 25 Hz. The acoustic waveform is generated by lateral muscle oscillations. The frequency of these oscillations should correspond to the resonant frequency of the muscle.[7] This explains why different muscles produce acoustic signals with varying resonant frequencies and therefore varying peak frequencies. Different forms of stimulation (e.g. tetanic *vs* single-twitch stimulation) mobilize different numbers of muscle fibres and generate different forms of contraction of the whole muscle, with different resonant frequencies.

Acceleromyography is the only method which has been used to measure neuromuscular block in the corrugator supercilii muscle.[5] [6] Originally, the acceleromyography probes were designed for use at the adductor pollicis muscle. The acceleration created by the contraction of the corrugator supercilii muscle is much smaller than that of the adductor pollicis muscle, with only minimal displacement of the acceleromyographic probe. The TOF watch SX provides a greater range of sensitivity than the TOF guard (Organon Instruments) to suit different muscles. Maximum sensitivity was set for all patients to ensure the detection of even small values of acceleration. In no patient, however, was a maximum effect greater than 90% block detected using the TOF watch SX. In seven of the 15 patients, time to reach 25% of control could not be detected using acceleromyography because the maximum effect was less than 75% of control. Phonomyography seems to be advantageous for small muscles, such as the corrugator supercilii muscle and the orbicularis oculi muscle, where little kinetic energy is created, because it is based on the measurement of sound generated not by the movement of an effector organ but the muscle contraction itself, i.e. the lateral movement of the muscle fibres.

In conclusion, phonomyography can be used to determine the onset and offset of neuromuscular blockade at the corrugator supercilii muscle. The best position for microphone positioning is in the middle of an area between the medial frontal line and the lateral part of the forehead, just above the eyebrow. Phonomyography and acceleromyography cannot be used interchangeably to determine neuromuscular block at the corrugator supercilii muscle. Acceleromyography demonstrates shorter onset time with lesser maximum effect and longer recovery from block in comparison with phonomyography.

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Effect of different pulses of nitric oxide on venous admixture in the anaesthetized horse

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Background. Dependent atelectatic lung areas open towards the end of inspiration when the lung opening pressure increases, and recollapse during expiration. We hypothesized that inhaled nitric oxide (NO) counteracts hypoxic vasoconstriction in these collapsing lung areas, resulting in increased pulmonary shunt perfusion.

Methods. We administered NO as a pulse and varied the pulse timing during inspiration in equine anaesthesia, where atelectasis develops regularly. Six spontaneously breathing standard breed trotters were studied under isoflurane anaesthesia in lateral recumbency. NO pulsed into the first 30% of inspiration (group NOp1) was assumed to affect open lung areas. To cover more open lung areas NO was then pulsed into the first 60% of inspiration (group NOp2). In a third group, administration between 50 and 80% of inspiration was aimed at the intermittently opening lung areas (group NOp3).

Results. With NOp1, venous admixture decreased by 8 (2)% (mean (SEM), P=0.045) and with NOp2 by 10 (1)% (P=0.01). With NOp3, venous admixture reduction was insignificant.

Conclusions. Pulsed administration of NO in early inspiration is optimal in reducing right to left vascular shunt in atelectatic equine lung. This reduction is positively correlated with the magnitude of the initial shunt. With administration in early inspiration, NO is mostly taken up by the lung. This prevents NO accumulation and NO_2 formation in rebreathing circuits. These findings may be important in humans when atelectasis occurs increasingly with overweight and age during anaesthesia, but also in postoperative intensive care and in ARDS.

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Nitric oxide (NO) delivered by inhalation induces vasodilatation in the lung.[1 2] This effect favours perfusion in ventilated lung areas, equating ventilation and perfusion distribution. The improved matching of ventilation and perfusion results in an increase in pulmonary artery oxygen partial pressure (Pa_{O_2}).[3] In humans with ventilation–perfusion mismatching, i.e. chronic obstructive pulmonary disease and adult respiratory distress syndrome (ARDS), inhalation of NO sometimes has no effect,[4 5] or even causes a decline in oxygenation.[6] These conflicting results are explained by NO inhalation occurring in lung compartments of low or no ventilation, counteracting hypoxic vasoconstriction, and increasing shunt perfusion.[6 7] Alveolar recruitment enhances the effect of NO therapy in ARDS patients where one-third of the lung may be aerated, but dependent lung areas are consolidated and atelectatic.[8–10] The boundary zone between the normal and altered areas where the lung opens and closes intermittently forms an area of low ventilation. As the inspired gas flow favours the open lung areas, the low ventilation areas are only reached towards the end of inspiration.[9] We hypothesize that NO, because of its high alveolar diffusion capacity, induces vasodilatation in

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the boundary zone where the ventilation is low, possibly increasing ventilation–perfusion mismatch and impairing gas exchange.[11]

In horses, atelectasis and ventilation–perfusion mismatch develop regularly during anaesthesia.[12] We therefore used equine anaesthesia to study the effect of NO delivered to various lung areas, in reducing shunt.

Material and methods

Six standard bred trotters with a mean (SEM) [range] age of 5 (1) [2–8] yr and weight of 513 (28) kg were examined. The local Ethics Committee for Animal Experiments approved the study.

Procedure and NO delivery

One hour after induction of anaesthesia, a period used for catheterization and to achieve stable anaesthesia, the first baseline readings were recorded and then NO was administered during the first 30% of inspiration (NOp1). Fifteen minutes after cessation of NOp1, a further baseline was recorded and NO was administered during the first 60% of inspiration (NOp2). After completion of NOp2, there was another 15-min resting period, followed by a new baseline recording. NO was then administered during 50–80% of inspiration (NOp3) to reach poorly ventilated areas of the lung. The response was recorded after 5 min of NO delivery in all delivery modes. As NOp3 involved a risk of a severe increase in shunt and hypoxaemia, no randomization of the order of administration of NO was performed.

NO was injected with a pulsed delivery device developed by Datex-Ohmeda Research Department, Helsinki, Finland. The device generates a NO pulse by regulating the flow of the NO-containing gas mixture for the required period. For the flow regulation, the device has a proportionally adjustable valve and a dose flow sensor. The NO pulse was injected during inspiration (NOp1, NOp2, or NOp3). A D-lite™ (Datex-Ohmeda) type flow sensor, dimensioned appropriately for the monitoring of horse ventilation, was used to synchronize the dose with breathing. The pulse was injected at the beginning of the tracheal tube to allow selective administration to different parts of the lungs. The NO supply was 2000 µl litre^{-1} NO in N_2 (AGA AB, Lidingö, Sweden).

Anaesthesia

During the12 h preceding anaesthesia, the horses were allowed to drink only water. Acepromazine 0.05 mg kg^{-1} was given intramuscularly approximately 30 min before induction of anaesthesia. An i.v. infusion of 7.5% guaifenesin was given until the horse became ataxic. Then anaesthesia was induced by the i.v. injection of thiopental 5 mg kg^{-1}. The trachea was intubated and the horses were positioned in lateral recumbency, and connected to a large-animal breathing circuit. Anaesthesia was maintained with spontaneous breathing of isoflurane in oxygen with a fresh gas flow of 5–6 litre min^{-1}. The end-tidal isoflurane fraction was 1.3–1.7%, adjusted for stable anaesthesia.

A thermodilution catheter (7F, Swan-Ganz) was inserted with an introducer kit (Arrow Int. Inc., Reading, PA, USA) through a right jugular vein to the pulmonary artery. This catheter was used for pulmonary artery pressure (PAP) and cardiac output ($\dot{Q}t$) measurement, and mixed venous blood sampling. A pigtail, multi-hole catheter (Cook Europe A/S, Söborg, Denmark) was inserted with a similar technique into the same jugular vein, advanced to the right ventricle, and retracted into the right atrium. This catheter was used as an injection port for $\dot{Q}t$ measurement. A catheter to measure mean arterial pressure (MAP) and to sample arterial blood was introduced percutaneously into the facial artery (Insyte-W, 18GA, Becton-Dickson, Ohmeda, Helsingborg, Sweden). The catheters were positioned under pressure-tracing guidance with simultaneous ECG monitoring and locked in position with a Luer-lock adaptor.

Monitoring

Expired NO was monitored with a chemiluminesence analyser prototype (Datex-Ohmeda) connected between the Y-piece and the point of NO administration. The analyser was calibrated with the mixture 100 µl litre^{-1} NO in N_2 (AGA AB) and with room air depleted of NO with a charcoal absorber. The signal rise time of the analyser was 200 ms, which allowed analysis of the expired breath pattern. The monitor was used to determine the end-tidal and peak expired NO fractions.

MAP and PAP were measured by pressure transducers positioned at the level of the sternal manubrium, which was considered to correspond to the level of the right atrium. These pressures, and also the inspired ($F\text{I}_{O_2}$) and expired ($F\text{E}_{O_2}$) gas oxygen fractions, respiratory rate (RR), tidal volume ($V\text{T}$), end-tidal carbon dioxide and oxygen fractions, and isoflurane fractions, were recorded on an AS/3 AM™ (Datex-Ohmeda) anaesthesia monitor.

Cardiac output was measured with the thermodilution technique (Cardiac Output Computer Model 9520 A, Edwards laboratory, Santa Ana, CA, USA); 20 ml 0°C 0.9% saline was injected into the right atrium through the pigtail catheter.

Arterial and central venous blood was obtained and analysed with a standard electrode technique (ABL 5, Radiometer, Copenhagen, Denmark). The arterial and venous ($P\bar{v}_{O_2}$) oxygen partial pressures were measured at standard electrode temperature (37°C) and the oxygen saturations (Sa_{O_2} and Sv_{O_2}, respectively) were calculated from the blood samples using the human P50 value 3.57 kPa, which is close to the equine value of 3.41 kPa.

To estimate the pulmonary shunt, venous admixture was calculated from the blood gas values using the method described by Berggren.[13]

Statistical analysis

Repeated measurement ANOVA was used to compare data within the group on different parts of the study. The Tukey honest significant difference test was used for post hoc comparisons and probability values were calculated. For all statistical calculations, the Statistica/w 5.0 software package (StatSoft Inc., Tulsa, OK, USA) was used. Results are given as mean values (SEM). In the analysis, the probability $P<0.05$ was considered as significant.

Results

Administration of NO did not affect ventilation, $\dot{Q}t$, or PAP, irrespective of the NO delivery period (Table 1). As a result of the longer pulse duration, the amount of NO delivered in NOp2 was twice that delivered in NOp1 and NOp3 to keep the NO fraction constant in the affected zones (Table 1). The NO fraction inspired during the pulse was calculated from the dose, respiration rate, NO pulse duration, and average inspiration flow (Table 1). There were no significant differences in the baseline values of venous admixture and Pa_{O_2} in NOp1, NOp2, and NOp3. The venous admixture was 27 (4), 29 (4), and 30 (3)%, respectively. The Pa_{O_2} was 27 (7), 22 (5), and 20 (4) kPa, respectively. With NOp1, the venous admixture decreased ($P=0.045$) and Pa_{O_2} increased ($P=0.033$). With NOp2, the venous admixture also decreased ($P=0.01$) and Pa_{O_2} increased ($P=0.021$). Despite the difference in the delivered amounts of NO in NOp1 and NOp2 ($P=0.011$), the effects of NO were equal. NOp3 did not improve venous admixture nor Pa_{O_2} The changes in venous admixture and Pa_{O_2} induced by the different delivery modes are presented in Figure 1.

When NO was delivered in early inspiration, the degree of reduction in venous admixture depended on its baseline value ($r=0.94$, $P=0.006$). The correlation for NOp1 is presented in Figure 2. Regression analysis shows that with this NO therapy, venous admixture could not be reduced when the baseline venous admixture was below 14%. However, baseline venous admixture above 14% could be reduced by 55%.

The expired peak NO fraction was higher during NOp2 ($P=0.047$) and NOp3 ($P<0.001$) than during NOp1. The end-tidal NO fraction was equally low in all NO delivery modes ($P=0.13$, Fig. 3). Because of the large NO expiration during NOp3, the fresh gas flow had to be increased to the minute ventilation to prevent rebreathing of NO from the circuit.

Discussion

The large degree of venous admixture (27–30%) and low Pa_{O_2} (20–27 kPa) in relation to the FI_{O_2} (1.0) indicate the presence of atelectasis in the horses in this study.[12] NO had a different effect on venous admixture when delivered in different phases of inspiration. Delivered during early inspiration, NO resulted in a reduction of venous admixture and improved arterial oxygenation. The venous admixture of the horses did not change significantly when NO was administered from 50 to 80% of inspiration, supporting the study hypothesis.

When NO was delivered in early inspiration, the decrease in venous admixture was positively correlated with its baseline value. A similar correlation was observed in our previous study of five horses in dorsal recumbency, where NO was only delivered during the first half of inspiration in three different procedures.[14] The venous admixture was reduced by 14% from a baseline of 37% when 9 μmol min^{-1} of NO was delivered during spontaneous breathing (reduction predicted from the line of identity of Fig. 2 is 13%); a reduction of 10% from a baseline of 32% occurred when 17 μmol min^{-1} of NO was delivered during spontaneous breathing (predicted value 10%) and a reduction of 7% from a baseline of 26% occurred when 30 μmol min^{-1} of NO was delivered during mechanical ventilation (predicted value 7%).[14] In another study of seven horses given NO at a constant 10 p.p.m. inspired concentration, the reduction in venous admixture fell below the line of identity with a baseline value of 21% and reduction of 1% (predicted value 4%).[15] This is comparable with the NO delivery given in NOp3 with corresponding figures of 30% and 5%, respectively (predicted value 9%).

Table 1 Tidal volume (V_T), respiration rate (RR), cardiac output ($\dot{Q}t$), mean pulmonary artery pressure (PAP), NO delivery rate, and fraction in the inhaled gas when administering NO during the first 30% (NOp1), during the first 60% (NOp2), and during the period between 50 and 80% of inspiration (NOp3). The NO fraction is calculated from the NO delivery, pulse duration, and ventilation

	NOp1		**NOp2**		**NOp3**	
	Control	**NO**	**Control**	**NO**	**Control**	**NO**
V_T (litre)	5.4 (0.8)	5.3 (0.8)	5.2 (0.7)	5.2 (0.8)	5.6 (1)	5.2 (0.7)
RR (min^{-1})	4.6 (1.2)	4.6 (1.1)	4.9 (1.4)	5.9 (2.2)	4.6 (1.4)	4.7 (1.3)
$\dot{Q}t$ (litre min^{-1})	28 (4)	28 (4)	30 (5)	32 (2)	25 (3)	33 (4)
PAP (cm H_2O)	28 (3)	27 (1)	29 (1)	27 (1)	30 (1)	30 (1)
NO (μmol min^{-1})		8.5 (1.8)		17.0 (4.4)		8.1 (2.0)
NO pulse (p.p.m.)		26 (1)		25 (2)		25 (2)

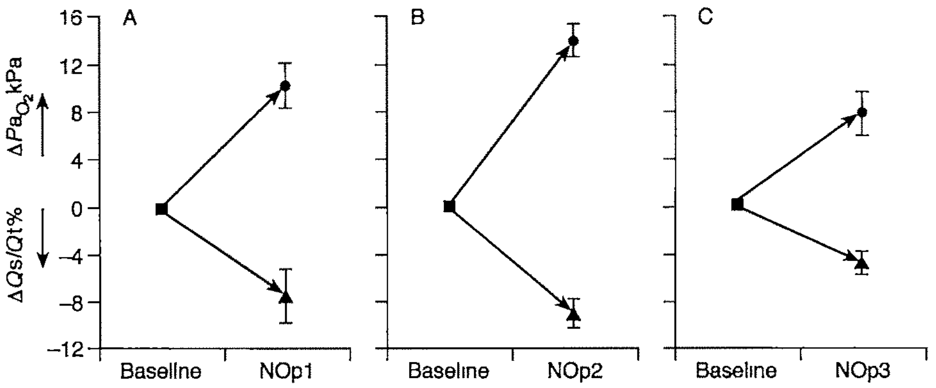

Fig 1 The change in venous admixture (*Qs/Qt*) and Pa_{O_2} when NO is delivered as a pulse in different parts of inspiration. Administration of NO during the first 30% (NOp1), during the first 60% (NOp2), and during the period between 50 and 80% of inspiration (NOp3), respectively (A) NOp1, (B) NOp2, and (C) NOp3

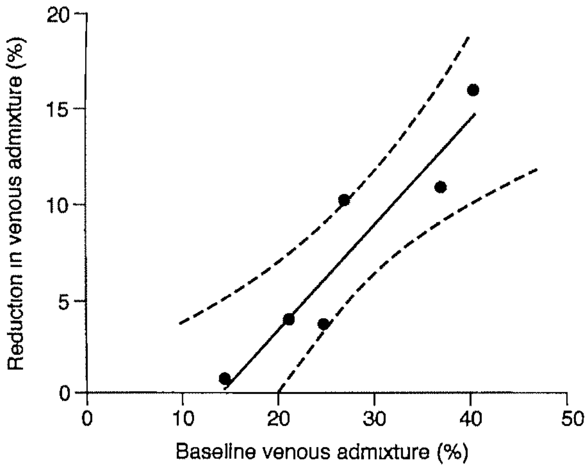

Fig 2 Correlation between the reduction in venous admixture and the venous admixture before NO delivery in the NOp1 mode (delivery during the first 30% of inspiration). The solid line is the regression line (r=0.94) and the dashed curves are 95% confidence range

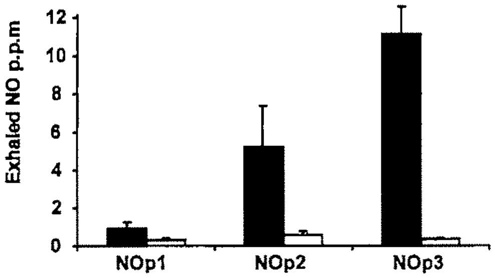

Fig 3 The exhaled NO peak (closed bar) and end-tidal NO (open bar) fractions in the different delivery modes (For explanation of NOp1, NOp2, and NOp3, see Fig. 1)

The reduction in venous admixture in human ARDS patients when NO is administered during the whole of inspiration is independent of the initial level,[4] estimations derived from that data suggest reduction of only 5% from 40% (14% predicted from Fig. 2). The smaller reduction in venous admixture when NO is delivered during the whole of inspiration may be explained by NO affecting the border zone, dilating the vessels affected by local hypoxic vasoconstriction, which counteracts any reduction in shunt caused by NO in the ventilated lung areas.

The proposed mechanism for the decrease in venous admixture with NO inhalation is vasodilatation as a result of decreased pulmonary vascular resistance. Even though the venous admixture was reduced with NO delivery during early inspiration in the present study, NO did not alter PAP or *Qt*. This surprising result may be because of vasoconstriction occurring in the zones not receiving NO. Perfusion redistribution without a change in PAP or *Qt* has also been observed in humans when NO is administered to one lung only.[16] This was associated with a significant increase in the pulmonary vascular resistance in the lung not receiving NO. Down-regulation of endogenous NO production in both lungs during unilateral administration of NO is proposed as one explanation of this finding. Another explanation involves vessel elasticity. Distension in regions receiving NO would allow the vessels to constrict elsewhere, because $\dot{Q}$t remains unaltered, thus preserving PAP.

The alveolar NO uptake determined experimentally in humans is 95–100%.[17] In simulation experiments, the uptake of NO administered in the first third of inspiration in pigs is 80–90%.[18] From the mean of the exhaled peak- and end-tidal fractions (Fig. 3), and the ventilation and NO delivery data in Table 1, the uptake in the NOp1 mode can be estimated at 92%, suggesting that NOp1 is delivered successfully to the alveolar region. When NO is delivered at a constant inspired concentration, the uptake rate decreases to 56[19] or 50–60%,[18] because of the expiration of NO from the anatomical dead space. In a rebreathing circuit, the expired NO is recycled leading to administration of an uncontrollable dose. In this circuit, the NO also reacts with oxygen forming NO_2. Hence in rebreathing circuits, NO should be delivered only in short pulses synchronous with early inspiration.

During human anaesthesia, the ventilation–perfusion ratio is high in the uppermost regions and low at the base of the lungs, which are subject to atelectasis.[20] Anaesthesia also induces at least a 70% increase in closing volume.[21] This increase is positively correlated with age and body mass index.[21 22] In morbidly obese patients, an observed 50% reduction in functional residual capacity compared with the pre-anaesthesia value has been found to be closely related to the development of atelectasis.[23 24] During general anaesthesia with mechanical ventilation, 75% of the impairment of arterial oxygenation may be explained by atelectasis and airway closure.[25] Common measures to compensate for the impairment are the use of a higher FI_{O_2} or increasing the positive end-expiratory pressure (PEEP). The development of atelectasis correlates with a high FI_{O_2}, and PEEP may increase the shunt, leading to deteriorating oxygenation.[25 26] Pulsed NO may provide a new method for maintenance of arterial oxygenation during anaesthesia, which could even reduce atelectasis formation by allowing a reduction in FI_{O_2}.

In conclusion, to reduce pulmonary shunt, NO delivered in pulses in early inspiration is the optimal method. With this type of administration, the degree of improvement correlates positively with the initial magnitude of the shunt. In rebreathing systems, NO should be delivered only in pulses to permit accurate dosing and to avoid NO_2 formation in the breathing circuit.

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BJA

LABORATORY INVESTIGATIONS

Role of nitric oxide and cyclooxygenase pathways in the coronary vascular effects of halothane, isoflurane and desflurane in red blood cell-perfused isolated rabbit hearts

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Background. The coronary vascular endothelium could mediate some of the coronary effects of halogenated anaesthetic agents. The role of the endothelial vasodilator substances nitric oxide (NO) and prostaglandins (PGs) in the coronary effects of halothane and isoflurane remains to be determined and has not been investigated for desflurane. In this study, the roles of NO and cyclooxygenase pathways in the coronary effects of halothane, isoflurane and desflurane were studied in isolated red blood cell-perfused rabbit hearts.

Methods. Rabbit hearts were perfused by a Langendorf technique with red blood cells mixed with modified Krebs–Henseleit buffer. Coronary blood flow (CBF), oxygen consumption and myocardial performance were evaluated during exposure to 0.5, 1 and 2 rabbit minimum alveolar concentrations of halothane, desflurane and isoflurane. Thereafter, the same protocol was applied with the addition of N^G-nitro-L-arginine (L-NNA), indomethacin or a combination of both inhibitors.

Results. Similar and significant increases in CBF were observed with increasing concentrations of isoflurane and desflurane. In contrast, CBF did not change with halothane. The combination of the two antagonists abolished desflurane-induced vasodilation, whereas it did not change the isoflurane-mediated increase in CBF. Halothane-induced vasoconstriction was observed in the presence of a combination of indomethacin with L-NNA.

Conclusions. Halothane and desflurane induce the release of vasodilating prostaglandins and NO in rabbit coronary arteries. In contrast, these mediators are not involved in the coronary vasodilating properties of isoflurane.

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The coronary effects of halogenated anaesthetic agents have been studied widely. These effects are partly due to interactions of the anaesthetic agent with endothelium-dependent mediators of coronary vascular control.[1] However, these agents have also been reported to produce direct effect on coronary vessels. Isoflurane and desflurane are both potent coronary vasodilators.[2] Halothane decreases coronary blood flow and myocardial metabolic demand in *in vivo* experiments[3] but induces moderate direct coronary vasodilation during direct intracoronary administration in canine hearts *in situ*[4] or in isolated arrested hearts.[5] In numerous investigations the potency of these coronary vasomotor effects has varied greatly according to the experimental protocol and remains controversial.

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The mechanisms of these coronary effects are complex and not yet fully understood. The vascular endothelium, in producing vasorelaxant substances such as nitric oxide (NO) and prostaglandins (PGs), might be involved in the vasomotor properties of halogenated agents. This hypothesis has been investigated mainly for halothane and isoflurane. Several conflicting results have led to the conclusion that endothelium-dependent vasodilating factors are released[6 7] or not released[8] by coronary vessels exposed to halothane or isoflurane. The role of vasodilating substances released from the endothelium in desflurane-induced coronary vasodilation has not been investigated.

Because endothelial functions may be severely impaired in several cardiovascular diseases that are frequently encountered in operative patients,[9] the magnitude of endothelium-dependent coronary vasomotricity related to exposure to halogenated agents needs to be evaluated. We studied (i) the nature of the direct effects of halothane, isoflurane and desflurane on the coronary vasculature in isolated red blood cell-perfused hearts, and (ii) whether the cyclooxygenase and NO pathways are involved in these effects.

Material and methods

The study was performed according to the regulations of the official edict issued by the French Ministry of Agriculture. Care of the animals was in agreement with the recommendations of the Declaration of Helsinki.

Heart preparation

New Zealand albino male rabbits (2–2.5 kg) were anaesthetized with ether. After thoracotomy, the heart and aortic arch were excised rapidly and immersed in cold isotonic saline solution. The pericardium was removed quickly under immersion and the aorta was prepared for cannulation. The heart was mounted on an aortic cannula. Aortic retrograde perfusion at a constant hydrostatic perfusion pressure (70–80 mm Hg) was started according to the Langendorf technique, as described in detail previously.[10] The apparatus was modified to reduce red blood cell sedimentation and filling pressure of the circuit and to enable the continuous recording of coronary blood flow. The column used to set the perfusion pressure was replaced by a syringe with a plunger containing mercury. The plunger was attached to a displacement transducer that controlled the speed of the coronary pump. Mean coronary perfusion pressure was recorded by means of a signal pressure obtained from a small catheter located above the aortic valves and connected to a pressure transducer (Statham P23Db: Spectramed, Bilthoven, The Netherlands). The whole apparatus was enclosed in a thermostatic chamber at 37°C. Coronary venous drainage was collected through a small catheter inserted in the pulmonary artery. A cannulated fluid-filled balloon connected to a pressure transducer (model P23Db; Statham) by a rigid catheter was placed in the left ventricle through a left atrial incision. The intraventricular balloon was inflated to maintain constant left ventricular volume. Left ventricular systolic and end-diastolic pressures (LVSP and LVEDP respectively) and heart rate were recorded, and maximal positive and negative left ventricular pressure derivatives (dP/dt_{max} and dP/dt_{min}) were derived electronically from the left ventricular signal. Because intraventricular volume was held constant, dP/dt_{max} and dP/dt_{min} were inotropic and lusitropic indices respectively. Atrial pacing maintained a constant heart rate.

Perfusate preparation

Packed human red blood cells (outdated for no longer than 1 week) stored at 4°C were used to prepare the perfusate. After centrifugation, the buffy coat and plasma were discarded and erythrocytes were washed twice with 150 mM NaCl solution. The blood was reconstituted by mixing red blood cells in a modified bicarbonate buffer containing (in mM) Na^+ 130, K^+ 5, free Ca^{2+} 2.5, $MgSO_4$ 1.17, $NaHCO_3$ 28, glucose 7 and human serum albumin 0.5%. The reconstituted blood was filtered through a 40 µm filter (model SQ 40S; Pall Ultipor: Pall Biomedical, St Germain en Laye, France) to eliminate polymorphonuclear cells and avoid microaggregate formation. The blood was then oxygenated using a membrane oxygenator with the following gas mixture: oxygen 20%, carbon dioxide 5%, nitrogen 75%. After rewarming (37°C), electrolyte concentrations were adjusted to achieve physiological concentrations and sodium bicarbonate was added to obtain standard acid balance.

Blood gas measurements

Arterial and coronary venous oxygen pressures ($P\bar{v}_{O_2}$), carbon dioxide pressures and pH were measured at 37°C (BGE; Instrumentation Laboratory, St Mandé, France). Arterial haemoglobin concentration and arterial and coronary venous saturations were measured with an oximeter (Co-oximeter 482; Instrumentation Laboratory). Arterial and coronary venous oxygen contents and myocardial oxygen consumption (Mv_{O_2}) were derived using standard formulae.

Administration of halogenated agents

A fraction of the perfusate was withdrawn and equilibrated through a second membrane oxygenator with halothane, desflurane or isoflurane over a 20-min period. Anaesthetic gases were administered using agent-specific vaporizers adjusted to deliver calculated anaesthetic concentrations. This circuit was connected to the perfusion circuit by a tap. The concentrations studied were 0.5, 1 and 2 rabbit minimum alveolar concentrations (MAC) for the three agents. The white rabbit MAC has been determined as

1.39% for halothane,[11] 8.9% for desflurane[12] and 2% for isoflurane.[11] Delivered anaesthetic concentration was monitored continuously using an infrared analyser (5250 RGM; Datex-Ohmeda, Limonest, France) connected to the oxygenator gas exit.

Halogenated anaesthetic concentration measurements in the blood perfusate

Blood samples (n=36) were withdrawn to determine the inflow perfusate concentrations corresponding to 0.5, 1 and 2 rabbit MACs of the three anaesthetics. Concentrations were measured by gas chromatography (Girdel S30 [Giravion Dorand, Suresnes, France] equipped with a Porapack Q [Touzart and Matignon, Courtaboeuf, France], 50–80 mesh, 200 cm column).

Experimental procedure

After aortic cannulation, each experiment included a 1-h period of stabilization. After baseline measurements had been made, infusion of the perfusate containing 0.5 MAC of halothane, desflurane or isoflurane was started. Arterial and venous samples were withdrawn for blood gas analysis during steady state in the last minute of exposure to anaesthetic. The control perfusate was reinfused and a return to control values was obtained before infusion of 1 and 2 MAC concentrations.

This procedure was applied to four different subgroups: (i) without inhibitor, (ii) in the presence of 30 µM N^G-nitro-L-arginine (L-NNA), (iii) with 1.4 µM indometacin, and (iv) with both antagonists. After the hearts had been allocated at random among the halogenated agents, they were further assigned randomly to one of the subgroups of antagonists.

We planned to perform 10 experiments in each subgroup. In total, 120 experiments were performed (four subgroups of 10 animals for each anaesthetic drug).

Drugs

L-NNA (Sigma, St Louis, MO, USA) was used as an inhibitor of NO synthase. Indomethacin (Sigma) was used as an inhibitor of the cyclooxygenase pathway. Indomethacin and L-NNA were added to the perfusate containing halogenated gas to obtain the appropriate concentrations. The concentrations used were 1.4 and 30 µM for indomethacin and L-NNA respectively, which correspond to values validated in this model.[13 14]

Statistical analysis

Comparisons between halothane, desflurane and isoflurane without inhibitors used two-way analysis of variance (NCSS; Deltasoft, Melan, France). The 'between' factor considered was the halogenated agent, and the 'within' factor was the concentration of the anaesthetic. When an interaction was found between the two factors, two-way analysis of variance was again performed for pairwise comparisons.

In the three groups, one-way analysis of variance was used to test whether the control condition was regained between different anaesthetic concentrations.

Two-way analysis of variance was performed to test the effects of inhibitors on the responses to halogenated agents. The 'between' factor considered was the inhibitor and the 'within' factor was the concentration of the anaesthetic. When an interaction was found, two-way analysis of variance was again performed for pairwise comparisons between the inhibitor subgroups (L-NNA, indomethacin and L-NNA+indomethacin) and the control group.

One-way analysis of variance was used to test whether the control condition was regained between each anaesthetic in each subgroup.

Results are expressed as mean (SD). For all tests, the level of significance was fixed at P<0.05.

Results

The final analysis considered 83 experiments: 26 in the subgroups without inhibitors (halothane, n=10; isoflurane, n=8; desflurane, n=8), 20 in the subgroups with L-NNA (halothane, n=6; isoflurane, n=7, desflurane, n=7), 19 in the subgroups with indomethacin (halothane, n=6; isoflurane, n=7; desflurane, n=6) and 18 in the subgroups with both antagonists (halothane, n=6; isoflurane, n=6; desflurane, n=6). Twenty-seven hearts were not included in the analysis because of poor experimental conditions (altered myocardial performance, unstable CBF or lack of complete return to control value between concentrations).

Electrolyte concentrations, pH, blood gases and haemoglobin values in the perfusates were not significantly different among groups (Table 1).

Measured anaesthetic concentrations for halothane 0.5, 1 and 2 MAC were 0.20 (0.05), 0.44 (0.02) and 1.00 (0.03) mM respectively, for desflurane 0.5, 1 and 2 MAC they were 0.75 (0.05), 1.45 (0.03) and 2.20 (0.05) mM respectively, and for isoflurane 0.5, 1 and 2 MAC they were 0.30 (0.02), 0.59 (0.03) and 1.28 (0.10) mM respectively.

Coronary effects of halothane, desflurane and isoflurane

CBF did not change with halothane (Fig. 1). In contrast, isoflurane and desflurane induced a significant increase in CBF (P<0.01) (Fig 1). This increase in CBF was similar for isoflurane and desflurane.

Similar concentration-dependent decreases in LVSP, dP/dt_{max}, dP/dt_{min} and $M\dot{V}o_2$ were observed with the three agents (Tables 2 and 3). The magnitude of these effects were not significantly different between the groups. LVEDP did

Table 1 Electrolytes, blood gases, glycaemia and haemoglobinaemia of the perfusates in the 12 subgroups. Results are mean (SD) No significant difference between subgroups. Indo=indomethacin

	Na^+ (mM litre^{-1})	K^+ (mM litre^{-1})	Ca^{2+} (mM litre^{-1})	Dextrose (mM litre^{-1})	pH	Pa_{O_2} (mm Hg)	Pa_{CO_2} (mm Hg)	HCO_3^- (mM litre^{-1})	Hb (g dl^{-1})
Halothane									
Without inhibitor	135 (6)	4.5 (0.9)	2.7 (0.3)	7 (1)	7.41 (0.09)	171 (6)	44 (6)	29 (3)	8.3 (0.6)
L-NNA	134 (5)	5.0 (0.5)	2.6 (0.2)	8 (1)	7.36 (0.10)	153 (12)	44 (5)	25 (2)	8.0 (0.3)
Indo	134 (7)	4.8 (1.0)	2.6 (0.2)	8 (1)	7.41 (0.05)	163 (10)	41 (5)	27 (2)	8.3 (0.7)
L-NNA+indo	135 (3)	4.3 (0.5)	2.5 (0.1)	7 (1)	7.41 (0.07)	152 (17)	47 (5)	31 (7)	8.0 (0.5)
Isoflurane									
Without inhibitor	137 (3)	4.4 (0.8)	2.5 (0.3)	7 (1)	7.42 (0.05)	163 (8)	44 (3)	27 (3)	8.7 (0.8)
L-NNA	135 (7)	4.2 (1.0)	2.4 (0.1)	7 (1)	7.42 (0.07)	165 (15)	39 (5)	26 (3)	8.8 (1.5)
Indo	139 (8)	4.9 (1.0)	2.6 (0.2)	7 (1)	7.42 (0.05)	146 (15)	38 (5)	26 (5)	8.2 (0.5)
L-NNA+indo	135 (2)	5 (1.7)	2.4 (0.1)	7 (1)	7.41 (0.05)	159 (12)	38 (3)	26 (3)	8.5 (1.9)
Desflurane									
Without inhibitor	136 (5)	4.4 (1.0)	2.6 (0.1)	7 (1)	7.39 (0.05)	163 (5)	44 (5)	28 (5)	8.2 (0.5)
L-NNA	138 (3)	5.0 (0.7)	2.6 (0.1)	7 (1)	7.45 (0.05)	161 (8)	43 (5)	32 (5)	7.7 (0.5)
Indo	133 (5)	5.0 (1.6)	2.5 (0.2)	7 (1)	7.41 (0.03)	154 (10)	41 (5)	27 (5)	7.9 (0.5)
L-NNA+indo	140 (5)	4.2 (1.0)	2.7 (0.1)	8 (1)	7.46 (0.04)	134 (17)	36 (5)	28 (5)	8.2 (0.3)

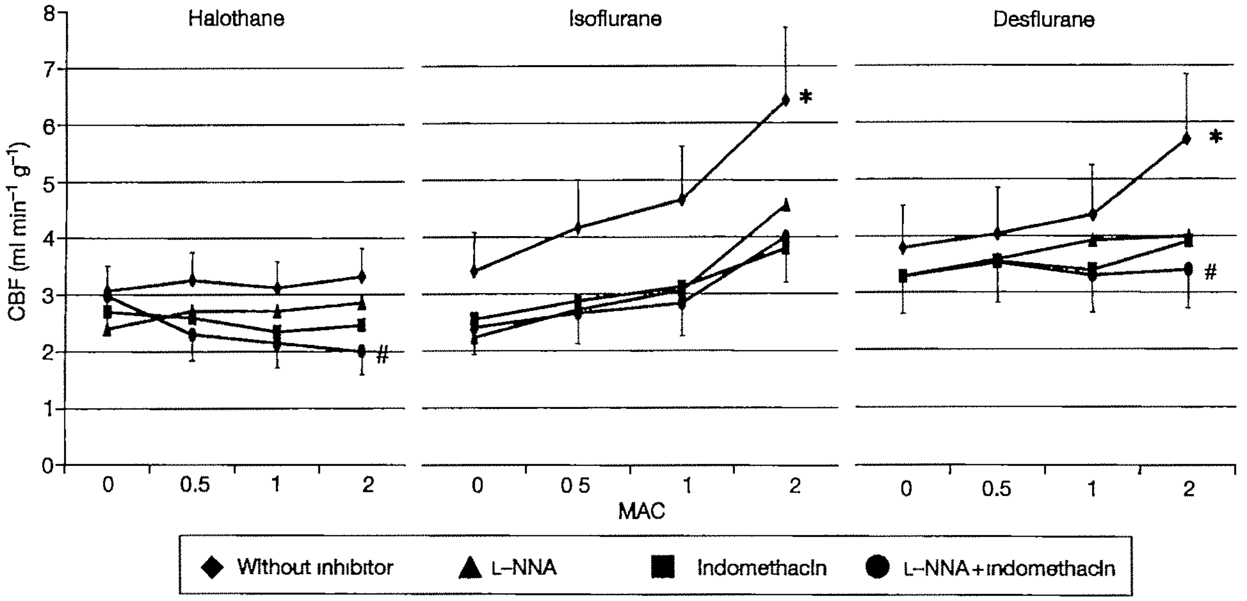

Fig 1 Effects of increasing concentrations of halothane, isoflurane and desflurane on CBF (mean and SD). CBF did not change with halothane. Isoflurane and desflurane induced a significant concentration-dependent increase in CBF (*$P<0.01$). The presence of both indomethacin and L-NNA modified the CBF response to halothane and desflurane ($P<0.01$) but did not change the dose–response curve for isoflurane.

not change with the different concentrations in the three groups (Table 2).

In all experiments, return to control values was obtained between each administration of the halogenated agent (Table 4).

Coronary effects of halothane, desflurane and isoflurane with endothelial inhibitors

Before administration of halogenated agents, L-NNA, indomethacin and L-NNA+indomethacin induced a significant decrease in CBF, by an average of 10 14 and 12% respectively ($P<0.05$). These decreases in CBF after exposure to the antagonists were similar for the three halogenated agents.

Indomethacin or L-NNA given alone did not change the coronary effects of halothane and desflurane (Fig. 1). In contrast, when both inhibitors were administered simultaneously, the coronary response to halothane and desflurane was changed significantly (Fig. 1). Indeed, halothane induced coronary vasoconstriction (Fig. 1) whereas the desflurane-induced vasodilation was prevented by the combination of indomethacin and L-NNA (Fig. 1). The

Table 2 Effects of halothane, desflurane, and isoflurane on LVSP (left ventricular systolic pressure) and LVEP (left ventricular end-diastolic pressure) Results are mean (SD) NS=not statistically significant

	Control	0.5 MAC	1 MAC	2 MAC	*P*	
					Between groups	**Concentration**
LVSP (mm Hg)					NS	<0.001
Halothane						
Without inhibitor	119 (16)	91 (19)	74 (12)	38 (9)		
L-NNA	108 (31)	85 (26)	71 (24)	43 (19)		
Indomethacin	107 (29)	89 (21)	71 (17)	43 (12)		
L-NNA+indomethacin	113 (17)	89 (17)	68 (14)	38 (10)		
Desflurane						
Without inhibitor	118 (20)	101 (20)	80 (17)	48 (11)		
L-NNA	97 (16)	87 (16)	68 (18)	40 (16)		
Indomethacin	107 (15)	93 (12)	73 (10)	52 (17)		
L-NNA+indomethacin	113 (17)	103 (12)	78 (7)	49 (5)		
Isoflurane						
Without inhibitor	113 (28)	94 (22)	73 (17)	45 (8)		
L-NNA	115 (18)	94 (18)	77 (16)	50 (18)		
Indomethacin	114 (16)	93 (16)	74 (13)	48 (10)		
L-NNA+indomethacin	101 (17)	85 (14)	64 (14)	40 (12)		
LVEDP (mm Hg)					NS	NS
Halothane						
Without inhibitor	6 (2)	7 (3)	6 (3)	5 (3)		
L-NNA	8 (5)	8 (5)	9 (5)	8 (7)		
Indomethacin	8 (1)	8 (2)	8 (2)	9 (5)		
L-NNA+indomethacin	6 (2)	6 (4)	6 (4)	6 (5)		
Desflurane						
Without inhibitor	7 (2)	8 (2)	6 (3)	7 (3)		
L-NNA	8 (3)	8 (3)	8 (3)	8 (3)		
Indomethacin	10 (5)	10 (5)	10 (5)	11 (5)		
L-NNA+indomethacin	7 (2)	7 (2)	6 (3)	6 (3)		
Isoflurane						
Without inhibitor	8 (3)	7 (3)	8 (4)	8 (3)		
L-NNA	7 (2)	7 (3)	6 (2)	7 (3)		
Indomethacin	9 (2)	9 (2)	9 (3)	9 (3)		
L-NNA+indomethacin	7 (2)	7 (1)	7 (1)	7 (1)		

coronary vasodilatory effect of isoflurane was not affected by either L-NNA or indomethacin given alone or by the combination of these inhibitors (Fig 1).

Similar concentration-dependent decreases in LVSP, dP/dt_{max}, dP/dt_{min} and Mv_{O_2} were observed with the three anaesthetics in the presence of the endothelial inhibitors (Tables 2 and 3). LVEDP did not change either during administration of the inhibitors or after administration of halogenated agents (Table 2).

In all experiments, return to control values was obtained between each administration of the halogenated agent (Table 4).

Discussion

This study shows that the three halogenated anaesthetic agents tested in isolated rabbit hearts perfused with blood cells have different effects on coronary blood flow and that the role of endothelium-derived vasodilating substances in these effects differs among these three agents.

Many factors could influence coronary responses to halogenated anaesthetic agents. Some of the conflicting results in the literature could be related to indirect haemodynamic effects of anaesthetic agents,[15] to the conditions of the experiment (isolated non-perfused pre-constricted or prevasodilated vascular rings versus whole perfused coronary network),[16] to the size of the coronary vessel under consideration,[16] to neurovegetative influences[3] or to the magnitude or rate of variation in concentration of halogenated anaesthetics.[17 18] Several of these factors can be ruled out in the present study, which was carried out in a non-ejecting isolated heart model with constant heart rate, preload and perfusion pressure, and without any interaction with the autonomic nervous system. As our group has demonstrated previously that the effect of anaesthetic agents on the coronary circulation and myocardial performance depends on the type of perfusate used in the experiment,[19] we chose to use isolated hearts perfused with a buffer containing red blood cells. The presence of red blood cells in the perfusate is important in the study of coronary circulation because the oxygen tension and content and baseline coronary blood flow are closer to physiological values [19 20] Previous work by our group has demonstrated that the endothelium-dependent and endothelium-independent coronary response,[21] as well as the coronary reserve,[22]

Table 3 Effects of halothane, desflurane, and isoflurane on dP/dt_{max} (maximal positive pressure derivative), dP/dt_{min} (maximal negative pressure derivative) and $M\dot{v}_{O_2}$ (myocardial oxygen consumption) Results are mean (SD). NS=not statistically significant

	Control	0.5 MAC	1 MAC	2 MAC	*P*	
					Between groups	**Concentration**
dP/dt_{max} (mm Hg s^{-1})					NS	<0.001
Halothane						
Without inhibitor	2108 (372)	1515 (385)	1178 (312)	615 (218)		
L-NNA	2075 (921)	1608 (710)	1333 (561)	650 (262)		
Indomethacin	1925 (668)	1491 (470)	1133 (352)	591 (181)		
L-NNA+indomethacin	2083 (431)	1516 (379)	1100 (262)	591 (122)		
Desflurane						
Without inhibitor	2156 (662)	1812 (688)	1481 (527)	900 (386)		
L-NNA	2264 (586)	1852 (369)	1339 (179)	716 (264)		
Indomethacin	2100 (512)	1780 (374)	1250 (181)	750 (122)		
L-NNA+indomethacin	2180 (614)	2000 (475)	1510 (286)	930 (124)		
Isoflurane						
Without inhibitor	2272 (896)	1860 (580)	1383 (397)	852 (298)		
L-NNA	2334 (520)	1876 (551)	1542 (467)	997 (427)		
Indomethacin	2250 (784)	1771 (628)	1435 (464)	921 (279)		
L-NNA+indomethacin	1736 (583)	1363 (428)	1209 (372)	761 (298)		
dP/dt_{min} (mm Hg s^{-1})					NS	<0.001
Halothane						
Without inhibitor	1438 (287)	1168 (316)	972 (274)	463 (154)		
L-NNA	1366 (418)	1116 (396)	950 (343)	466 (193)		
Indomethacin	1350 (629)	1100 (433)	850 (534)	408 (151)		
L-NNA+indomethacin	1641 (320)	1241 (245)	925 (215)	416 (110)		
Desflurane						
Without inhibitor	1537 (518)	1375 (482)	1162 (456)	700 (301)		
L-NNA	1304 (332)	1150 (200)	951 (126)	498 (211)		
Indomethacin	1520 (335)	1320 (335)	1000 (227)	600 (139)		
L-NNA+indomethacin	1510 (418)	1460 (382)	1175 (245)	690 (95)		
Isoflurane						
Without inhibitor	1388 (626)	1202 (476)	929 (366)	557 (236)		
L-NNA	1801 (625)	1491 (572)	1219 (491)	729 (401)		
Indomethacin	1550 (615)	1314 (615)	1042 (403)	707 (232)		
L-NNA+indomethacin	1301 (411)	997 (482)	906 (291)	492 (220)		
$M\dot{v}_{O_2}$ (ml min^{-1}100 g^{-1})					NS	<0.001
Halothane						
Without inhibitor	7.9 (1.9)	5.7 (2.5)	5.3 (2.5)	3.9 (1.3)		
L-NNA	6.5 (1.5)	5.8 (2.2)	6.0 (2.2)	4.9 (2.2)		
Indomethacin	7.4 (1.5)	6.3 (2.0)	6.1 (2.2)	5.6 (2.4)		
L-NNA+indomethacin	8.9 (2.0)	4.3 (1.5)	3.9 (1.5)	3.4 (1.9)		
Desflurane						
Without inhibitor	8.9 (1.1)	6.9 (2.2)	6.0 (1.4)	5.0 (2.2)		
L-NNA	9.6 (2.6)	8.1 (2.2)	8.0 (2.1)	7.4 (2.1)		
Indomethacin	8.1 (1.2)	7.8 (1.9)	5.5 (1.2)	4.6 (1.0)		
L-NNA+indomethacin	10.2 (4.9)	8.3 (1.9)	7.4 (2.5)	6.7 (2.0)		
Isoflurane						
Without inhibitor	7.0 (1.7)	6.0 (2.2)	4.0 (2.2)	4.0 (2.8)		
L-NNA	5.0 (2.6)	4.0 (1.8)	3.2 (2.4)	2.6 (1.3)		
Indomethacin	6.4 (1.3)	5.8 (2.3)	5.6 (2.3)	4.1 (1.8)		
L-NNA+indomethacin	6.6 (2.0)	5.5 (1.9)	4.7 (1.5)	3.4 (1.7)		

are preserved in the blood-perfused model. Furthermore, a recent study demonstrated that the release of endothelial mediators by the vessels may be affected markedly by the absence of red blood cells.[23]

The rabbit coronary circulation is appropriate for the study of the influence of NO and PG pathways in the vasodilatory effects of anaesthetic agents because these mediators have been clearly demonstrated to be involved in the rabbit endothelium-dependent coronary vasodilation.[13 14 24 25]

In the present study, we found that both myocardial performance and oxygen consumption decreased similarly with the three anaesthetic agents tested. This allowed us to exclude the possibility that the observed differences in coronary blood flow could be related to differences in myocardial metabolic demand.

In agreement with other studies in *in vivo* models[2] and in isolated hearts,[26] isoflurane increased coronary blood flow significantly in our model. We observed an increase in CBF close to that reported by Crystal and colleagues after gradual coronary administration of isoflurane in chronically instrumented dogs.[18] The mechanism of the vasodilatory action of isoflurane

Table 4 Return to control values, between 0.5 and 1 MAC (Return 1) and between 1 and 2 MAC (Return 2). LVSP=left ventricular systolic pressure, LVEDP=left ventricular end-diastolic pressure. No significant change for the three groups and for the different subsets of experiments between Control, Return 1 and Return 2 Values are mean (SD)

	Halothane			Isoflurane			Desflurane		
	Control	Return 1	Return 2	Control	Return 1	Return 2	Control	Return 1	Return 2
LVSP (mm Hg)									
Without inhibitor	119 (16)	115 (16)	110 (16)	113 (28)	111 (31)	106 (28)	118 (20)	115 (20)	109 (17)
L-NNA	108 (31)	102 (27)	96 (27)	115 (18)	109 (23)	103 (18)	97 (16)	102 (21)	95 (18)
Indomethacin	107 (29)	102 (27)	96 (22)	114 (16)	109 (16)	106 (16)	107 (15)	101 (14)	91 (10)
L-NNA+indomethacin	113 (17)	103 (17)	99 (17)	101 (17)	89 (17)	90 (14)	113 (17)	111 (14)	102 (15)
LVEDP (mm Hg)									
Without inhibitor	6 (2)	6 (3)	6 (3)	8 (3)	7 (4)	7 (5)	7 (2)	7 (2)	6 (3)
L-NNA	8 (3)	8 (4)	8 (6)	7 (2)	6 (2)	6 (2)	8 (3)	11 (5)	10 (5)
Indomethacin	8 (1)	8 (3)	8 (6)	9 (2)	9 (3)	9 (3)	10 (5)	9 (5)	9 (6)
L-NNA+indomethacin	6 (2)	(6)	6 (6)	7 (2)	6 (1)	6 (2)	7 (2)	7 (3)	7 (3)

remains to be determined. It has been suggested that isoflurane stimulates the release of a vasodilating prostanoid from the isolated rat aortic vascular endothelium.[17] In rabbit coronary microvessels, isoflurane vasodilation of conductance arteries is mediated by endothelium-dependent PGs and NO, whereas isoflurane causes endothelium-dependent constriction in the distal part of the coronary vascular bed.[7] In indomethacin-treated rats, part of the coronary vasorelaxant effect of isoflurane has been ascribed to the secretion of NO.[6] However, other investigators came to the opposite conclusion—that NO does not mediate coronary vasodilation induced by isoflurane.[8] This discrepancy could be related to differences in experimental protocol (whole animal or isolated vascular rings) or to differences in regional circulation or to the size of the coronary vessels.[7] Indeed, Park and colleagues demonstrated heterogeneous vasomotor responses, involving different endothelium-dependent mechanisms, according to the size of the coronary vessels and their preconstricted state.[7 16] In the present study, we investigated the global effect of halogenated agents on the whole coronary network. The increase in CBF mediated by isoflurane was not affected by the presence of indomethacin or L-NNA, either alone or in combination. Consequently, it can be concluded that the isoflurane-induced increase in CBF was not mediated by NO or PGs. This result is in accordance with that found by Crystal and colleagues in chronically instrumented dogs.[8] Many recent studies have suggested that isoflurane-induced coronary vasodilation may be related to opening of the adenosine triphosphate-sensitive potassium channels (K_{ATP} channels).[27 28]

We found that the coronary vasodilating ability of desflurane was similar to that of isoflurane. This assumption is in accordance with the observations of others.[2 29 30] The mechanisms underlying the coronary vasodilating properties of desflurane have been poorly studied. In particular, the role of endothelium-dependent mechanisms remains to be determined. In the present study, we found that simultaneous administration of indomethacin and L-NNA completely prevented the increase in CBF induced by desflurane. Interestingly, this effect was not blocked by either indomethacin or L-NNA when administered alone. This point deserves further discussion. As shown by Berti and colleagues in the coronary circulation of rabbits, it is possible that the effect of the inhibition of either the NO or the cyclooxygenase pathway can be counterbalanced by amplification of the other.[25] In conscious dogs, enhancement of the cyclooxygenase pathway may supplement altered NO synthesis to allow vasodilation of the coronary bed.[31] The hypothesis that L-NNA and indomethacin given alone are not effective in blocking the NO and cyclooxygenase pathways respectively can be ruled out because we demonstrated a significant decrease in CBF (corresponding to an increase in coronary resistance) after administration of these antagonists. As has been described in other models, no additive effect on basal resistance is observed when these two inhibitors are administrated simultaneously.[32]

Unchanged CBF with halothane has already been shown in numerous studies.[3 33] We observed a decrease in CBF in the presence of NO and PG synthase inhibitors. In isolated rat aortic vascular rings, Stone and Johns demonstrated that halothane induced vasoconstriction in the presence of indomethacin.[17] In addition, the vasorelaxant effect of halothane was found to be abolished by indomethacin in rat diaphragm vessels.[34] It has been shown that blockade of the NO pathway induces a significant increase in coronary resistance during halothane exposure.[6] Thus, it can be hypothesized that the stability of CBF under halothane anaesthesia can be related to a balance between two opposite effects: an endothelium-dependent vasodilatory effect, which is blunted by the endothelial inhibitors, and a vasoconstrictive effect. This vasoconstrictive effect may be related indirectly to its negative inotropic property[5] or to the release of an endothelium-dependent constricting factor, as has been shown recently in the pulmonary circulation.[35] A direct vasoconstricting effect of halothane on coronary vascular smooth muscle is unlikely because halothane-induced vasodilation was found in coronary vessels without endothelium.[36]

In conclusion, marked differences in the mechanisms of the coronary response to halothane, desflurane and isoflurane were found in the rabbit heart. The cyclooxygenase and NO pathways are not involved in isoflurane-induced vasodilation. In contrast, a major part of the vasodilation induced by desflurane is related to the simultaneous release of vasodilating PGs and NO. In the presence of indomethacin and L-NNA, halothane induced coronary vasoconstriction.

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Inhaled olprinone improves contractility of fatigued canine diaphragm

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Background. Diaphragmatic fatigue is implicated as a cause of respiratory failure. This study was undertaken to evaluate the effects of inhaled olprinone, a newly developed phosphodiesterase III inhibitor, on the contractility of fatigued diaphragm in dogs.

Methods. Diaphragmatic fatigue was induced by intermittent supramaximal bilateral electrophrenic stimulation at a frequency of 20 Hz stimulation applied for 30 min. When fatigue was established, group I (n=8) received inhaled vehicle; group II (n=8) received inhaled olprinone 1 mg; group III (n=8) received inhaled olprinone 2 mg. Diaphragmatic contractility was assessed by transdiaphragmatic pressure (Pdi, cm H_2O).

Results. In the presence of fatigue, in each group, Pdi at low-frequency (20 Hz) stimulation decreased from baseline values (P<0.05), whereas Pdi at high-frequency (100 Hz) stimulation did not change. In groups II and III, during olprinone administration, Pdi at both stimuli increased from fatigued values (20 Hz stimulation: group II (mean (SD)) 10.8 (1.0) to 12.5 (1.3), group III 10.9 (1.7) to 15.0 (3.0); 100 Hz stimulation: group II 20.1 (1.9) to 22.6 (1.3), group III 20.6 (2.0) to 24.5 (2.0), P<0.05). The increase in Pdi was larger in group III than in group II (P<0.05).

Conclusions. Inhaled olprinone produces a dose-dependent improvement in contractility of fatigued canine diaphragm.

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Phosphodiesterase (PDE) III inhibitors have been evaluated for therapeutic potential in the treatment of congestive heart failure.[1 2] In addition to these pharmacological properties, we have shown that amrinone, milrinone, and olprinone administered intravenously (i.v.) improve contractility of fatigued diaphragm that is implicated as a cause of respiratory failure, and that olprinone is most efficacious against diaphragmatic fatigue.[3–5] Recently, Myou and colleagues[6] have demonstrated that inhaled olprinone exhibits bronchodilater activity in asthmatic patients. However, there have been no reports investigating the effects of inhaled olprinone on contractility of fatigued diaphragm. The purpose of the present study was to examine the efficacy of inhaled olprinone for the improvement of diaphragm muscle function in dogs.

Methods

The procedure was approved by our animal research committee, and the care of animals was in agreement with guideline for ethical animal research. Twenty-four healthy mongrel dogs weighing 10–15 kg were anaesthetized with pentobarbitone (25 mg kg^{-1} loading dose plus 2 mg kg^{-1} h^{-1} maintenance dose) i.v. to abolish spontaneous movement. Muscle relaxants were not used. Animals were placed in the supine position, their tracheas were intubated with a cuffed tracheal tube, and the lungs were ventilated mechanically with a mixture of oxygen and air ($F\text{I}_{O_2}$=0.4) to maintain Pa_{O_2}13.3 kPa, Pa_{CO_2}=4.7–5.3 kPa, and pHa=7.35–7.45. The right femoral artery was cannulated to monitor arterial pressure and to obtain blood gas samples for blood gas

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analysis. Arterial blood gas tensions were measured every 30 min. The right femoral vein was cannulated to administer fluids (Ringer's lactate solution 10 ml^{-1} kg^{-1} h^{-1}), pentobarbitone and bicarbonate to maintain plasma HCO_3^- concentration within normal range. Rectal temperature was monitored continuously and maintained at 37 (1)°C.

The phrenic nerves were exposed bilaterally at the neck, and stimulating electrodes were placed around them. Transdiaphragmatic pressure (Pdi) was measured using two thin-walled latex balloons: one positioned in the stomach, the other in the middle third of the oesphagus. Balloons were connected to a differential pressure transducer and an amplifier. Supramaximal electrical stimuli (10–15 V) of 0.1 ms duration were applied for 2 s at low-frequency (20 Hz) and high-frequency (100 Hz) stimulation with an electrical stimulator. The isometric contractility of the diaphragm was evaluated by measuring maximal Pdi after airway occlusion at FRC. Transpulmonary pressure (Ptp), the difference between airway and oesophageal pressures, was maintained by maintaining same lung volume before each phrenic stimulation. End-expiratory diaphragmatic geometry and muscle fibre length during contraction were kept constant by placing a close-fitting plaster cast around the abdomen and lower one-third of the rib cage. Electrical activity of crural (Edi-cru) and costal (Edi-cost) parts of the diaphragm was recorded by two pairs of fishhook electrodes placed through a midline laparotomy: electrodes were positioned into the anterior portion of crural part near the central tendon and the anterior portion of costal part (away from the zone of apposition) in the left hemidiaphragm. Each pair was placed in parallel fibres 5–6 mm apart. The abdomen was then sutured in layers. The signal was rectified and integrated with a leaky integrator with a time constant of 0.1 s, and was regarded as the integrated diaphragmatic electrical activity (Edi-cru, Edi-cost).

Twenty-four dogs were randomly divided into three groups of eight each. After measuring the pre-fatigued (baseline) values of Pdi, Edi-cru, Edi-cost, and haemodynamic variables, in each group, diaphragmatic fatigue was induced by intermittent supramaximal bilateral electrophrenic stimulation applied for 30 min at a frequency of 20 Hz, an entire cycle of 4 s, and a duty cycle of 0.5 (i.e. low-frequency fatigue).[7] Olprinone 1 mg (group II), olprinone 2 mg (group III), or vehicle (group I) was inhaled from DeVilbiss 646 nebulizer (DeVilbiss Co., Somerset, PA, USA) operated by compressed air at 5 $litre^{-1}$ min^{-1}. The nebulizer output was 0.14 ml min^{-1}. The dose of olprinone chosen in this experiment was based on the study of Myou and colleagues.[6] Thirty minutes after the start of inhalation, in each group, Pdi, Edi-cru, Edi-cost, heart rate, and mean arterial pressure (MAP) were measured.

Values are mean (SD). Statistical analysis was performed by ANOVA for repeated measurements with Bonferroni's adjustment for multiple comparison and Student's *t*-test, where appropriate. A *P* value of <0.05 was considered significant.

Results

No differences in haemodynamic variables and Pdi in the pre-fatigued (baseline) period were observed among the three groups. With an inhalation of olprinone in group III, increases in heart rate ($P<0.05$) and decreases in MAP ($P<0.05$) were observed. In groups I and II, there were no haemodynamic changes throughout the experiment (Table 1).

Pdi values at different stages and changes of Edi-cru and Edi-cost (%Edi-cru and %Edi-cost, respectively) from baseline values are shown in Table 1. Three groups were comparable with regard to Pdi to each stimulus during baseline condition. In each group, after producing fatigue, Pdi at low-frequency (20 Hz) stimulation decreased from baseline values ($P<0.05$), whereas Pdi at high-frequency (100 Hz) stimulation did not change. In groups II and III, Pdi at both stimulation frequencies increased from fatigued values ($P<0.05$) during olprinone inhalation. The increase in Pdi to each stimulus was larger in group III than in group II ($P<0.05$). In group I, the speed of recovery from fatigue was slower at 20 Hz stimulation than at 100 Hz stimulation. No changes in %Edi-cru and %Edi-cost were observed throughout the study in any group.

Discussion

The pressure generated by the diaphragm (Pdi) after a given electrical stimulus depends on its length and geometry.[8] A major determinant of length and geometry of the diaphragm is lung volume. In this study, lung volume was strictly controlled, because the airway was occluded at end-expiratory lung volume during the measurements and the end-expiratory Ptp was maintained constant before each stimulus. The deformation of thoracoabdominal structures was also avoided by placing a cast around the abdomen and lower one-third of the rib cage. Therefore, changes in Pdi observed in this experiment can be regarded as the result of changes in diaphragmatic contractility.

Hypoxaemia, hypercapnia, and metabolic acidosis decrease contractility of the diaphragm.[9 10] The Pa_{O_2}, Pa_{CO_2}, pHa, and HCO_3^- concentration were controlled within normal ranges in this study. Therefore, these factors that could have affected diaphragmatic contractility were excluded. In addition, it has been reported that pentobarbitone, at the dose used in this experiment, does not affect diaphragmatic contractility.[11] This was also in accordance with our results in group I showing no change in Pdi

Low-frequency fatigue is of particular clinical importance because the spontaneous, natural rate of phrenic nerve discharge is mainly in the low-frequency ranges (i.e. 5–30 Hz).[12] Therefore, the effect of inhaled olprinone on contractility in fatigued diaphragm induced by 20 Hz

Table 1 Changes in haemodynamics, Pdi (cm H_2O), and %Edi values are mean (SD) HR=heart rate, MAP=mean arterial pressure, Pdi=transdiaphragmatic pressure, Edi-cru=integrated electrical activity of the crural part of diaphragm, Edi-cost=integrated electrical activity of the costal part of diaphragm $^*P<0.05$ *vs* baseline, $^\dagger P<0.05$ *vs* fatigued; $^\ddagger P<0.05$ *vs* group I, $^+P<0.05$ *vs* group II

Variable	Group	Baseline	Fatigued	Study drug
Haemodynamics HR (beat min^{-1})	I	146 (11)	144 (7)	145 (11)
	II	144(10)	145 (8)	149 (10)
	III	145 (8)	144 (7)	157 (7)*†‡
MAP (mm Hg)	I	138 (9)	137 (13)	141 (8)
	II	140 (10)	138 (11)	136 (8)
	III	142 (7)	141 (6)	129 (9)*†‡
Pdi (cm H_2O) 20 Hz stimulation	I	14.2 (1.8)	10.6 (1.3)*	11.0 (1.7)*
	II	14.4 (1.5)	10.8 (1.0)*	12.5 (1.3)†‡
	III	14.3 (2.0)	10.9 (1.7)*	15.0 (3.0)†‡
100 Hz stimulation	I	20.9 (2.4)	20.6 (3.0)	20.3 (2.8)
	II	20.6 (2.3)	20.1 (1.9)	22.6 (1.3)
	III	21.1 (2.0)	20.6 (2.0)	24.5 (2.0)$^{*\dagger\ddagger+}$
%Edi-cru 20 Hz stimulation	I	100.0 (0.0)	97.9 (6.0)	99.1 (7.4)
	II	100.0 (0.0)	97.9 (6.0)	99.8 (5.4)
	III	100.0 (0.0)	96.9 (8.8)	100.9 (12.9)
100 Hz stimulation	I	100.0 (0.0)	97.8 (3.1)	99.5 (6.1)
	II	100.0 (0.0)	99.4 (4.8)	99.4 (4.8)
	III	100.0 (0.0)	96.5 (4.9)	100.0 (3.4)
%Edi-cost 20 Hz stimulation	I	100.0 (0.0)	101.3 (8.3)	103.9 (10.4)
	II	100.0 (0.0)	97.9 (6.0)	100.9 (12.9)
	III	100.0 (0.0)	97.3 (13.3)	101.4 (11.8)
100 Hz stimulation	I	100.0 (0.0)	100.1 (2.4)	100.1 (2.4)
	II	100.0 (0.0)	99.4 (4.8)	100.0 (3.4)
	III	100.0 (0.0)	98.4 (3.3)	99.4 (3.2)

stimulation (i.e. low-frequency fatigue) was examined. Following a fatigue-producing period, in each group, Pdi at 20 Hz stimulation decreased from baseline values ($P<0.05$), whereas Pdi at 100 Hz stmulation did not change. The results of group I, in which Pdi was observed without inhalation of olprinone in fatigued diaphragm, showed that the speed of recovery from fatigue was relatively slower at 20 Hz stimulation than at 100 Hz stimulation, and also showed that Edi to each stimulus did not change. This was in agreement with previous studies by us.[3–5]

PDE III inhibitors—including amrinone, milrinone, and olprinone—administered i.v. at doses used clinically have been shown previously to increase contractility of fatigued diaphragm.[3–5] Amrinone (10 μg kg^{-1} min^{-1}) increases Pdi by 55% at 20 Hz stimulation and by 9% at 100 Hz stimulation; milrinone (0.5 μg kg^{-1} min^{-1}) increases Pdi by 69% and by 23% at each stimulus; olprinone (0.3 μg kg^{-1} min^{-1}) increases Pdi by 85% and by 35% at each stimulus.[3–5] Thus, PDE III inhibitors affect Pdi at 20 Hz stimulation more when compared with Pdi at 100 Hz stimulation. We have no explanation for this difference, but olprinone is more effective than amrinone or milrinone for the augmentation of contractility in fatigued diaphragm. In the present study, Pdi at 20 and 100 Hz stimulation increased from fatigued values ($P<0.05$) when olprinone was administered by inhalation in groups II and III. The increase in Pdi at both stimuli was also larger in group III than in group II ($P<0.05$). These observations suggest that inhaled olprinone, in addition to i.v. olprinone, improves contractility of fatigued diaphragm, in a dose-related manner.

Diaphragmatic blood flow is an important determinant factor in diaphragm muscle function[12] and is also maintained relatively constant within a certain limit of perfusion pressure.[13] When MAP increases to >9.3 kPa, diaphragmatic blood flow is not reduced.[14] In this study, however, MAP <9.3 kPa was not observed with an inhlation of olprinone in groups II and III. Therefore, the decrease in MAP during olprinone inhalation would not affect diaphragmatic contractility. Additionally, cardiovascular effects were not evident in group II (no changes in heart rate and MAP) during olprinone inhalation while the effects on Pdi at both stimuli were significant. This suggests that the action of inhaled olprinone on heart rate and MAP are not important for its effects on contractility in the fatigued diaphragm.

Olprinone, administered i.v., increases contractility of cardiac muscle by selectively inhibiting PDE III and accumulating cyclic AMP intracellularly, which, in turn, induces the activation of Ca^{2+} transport from the sarcoplasmic reticulum.[14] In a previous report by us,[5] to clarify the mechanism responsible for the effects of olprinone administered i.v. on contractility of fatigued diaphragm, combined olprinone and nicardipine, a calcium antagonist which inhibits Ca^{2+} influx into diaphragmatic muscle,[15] was administered. Augmentation of Pdi by olprinone was abolished by administation nicardipine, suggesting that olprinone may increase contractility of fatigued diaphragm by influencing Ca^{2+} transport across the cell membrane. Why the fatigued diaphragmatic contractility was enhanced during olprinone inhalation is not known. The mechanisms of action of inhaled olprinone in the improvement of contractility in fatigued diaphragm may be similar to that of i.v. olprinone. However, further studies with inhaled olprinone and nicardipine are required.

In summary, inhaled olprinone produced a dose-dependent improvement, in contractility of fatigued canine diaphragm.

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Effects of propofol on lactate accumulation and oedema formation in focal cerebral ischaemia in hyperglycaemic rats

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Background. In cerebral ischaemia, hyperglycaemia brings about severe lactate accumulation and neuronal damage when compared with normoglycaemia. Propofol has been known to suppress glucose metabolism in the brain and possess neuroprotective properties in cerebral ischaemia. Therefore, in this study we examined if propofol could attenuate lactate accumulation and neuronal damage in cerebral ischaemia under hyperglycaemic conditions.

Methods. Ten male wistar rats were divided into two experimental groups: low-dose (~12 mg kg^{-1} h^{-1}) and high-dose (~60 mg kg^{-1} h^{-1}) propofol groups (n=5 for each). Following injection of 2 g kg^{-1} glucose intraperitoneally, the middle cerebral artery was occluded for 1 h, and then reperfused for the following 2 h. Lactate accumulation and oedema formation were estimated consecutively using nuclear magnetic resonance (NMR) techniques.

Results. Lactate accumulation and oedema formation increased continuously during ischaemia and reperfusion in the low-dose propofol group, which was attenuated in the high-dose propofol group. Lactate/NAA (*N*-acetylaspartate) ratio (as an index of lactate accumulation) 60 and 120 min after reperfusion were 2.67 and 3.26 in low-dose group and 0.30 and 0.10 in high-dose group. For NMR images the number of pixels with a low average diffusion coefficient (an index of the oedema formation), 60 and 120 min after reperfusion were 250.0 and 317.8 in low-dose group, and 16.0 and 12.4 in high-dose group.

Conclusion. High-dose propofol attenuated lactate accumulation and oedema formation in cerebral ischaemia in hyperglycaemic rats.

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Pre-ischaemic hyperglycaemia aggravates brain damage following ischaemia.[1–3] Hyperglycaemia significantly worsens both intracellular brain acidosis and mitochondrial function in the ischaemic penumbra.[4] Hyperglycaemia increases the magnitude and topographic extent of tissue lactic acidosis and infarct size following transient cerebral ischaemia.[5] In a previous study, we showed the extent of lactate accumulation and oedema formation in transient focal cerebral ischaemia was more severe in rats under hyperglycaemic conditions than those under normoglycaemic conditions using nuclear magnetic resonance (NMR).[6] Further, it was demonstrated that isoflurane did not attenuate the adverse effects of hyperglycaemia; nevertheless, isoflurane was reported to improve neurological outcome after incomplete cerebral ischaemia in rats.[7]

Propofol, an i.v. anaesthetic, was reported to possess neuroprotective properties,[8–10] which are greater than isoflurane in cerebral ischaemia reperfusion injury.[10] Furthermore, propofol was shown to suppress cerebral glucose utilization[11 12] more effectively than isoflurane.[13] Therefore, propofol may attenuate ischaemia-induced neuronal damage aggravated by hyperglycaemia.

In the present study, the effects of propofol on the accumulation of lactate and the formation of oedema in the brain during ischaemia and reperfusion were examined in hyperglycaemic rats, using NMR technique.

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Material and methods

Animal preparation

The study was approved by the Animal Research Committee of Kyoto University, Faculty of Medicine. Experiments were performed on 10 adult spontaneously hypertensive rats (SHR) weighing 310–360 g and aged 12–15 weeks. Rats were allowed free access to water and laboratory chow before experimentation. Each rat was anaesthetized with 2% halothane in 50% oxygen and balanced nitrogen through a facemask. A remote controlled rat intraluminal suture middle cerebral artery occlusion (MCAO) model was prepared as described by Röther and colleagues.[14] The occluding device was prepared with a 4-0 monofilament nylon suture 5-cm long, the tip of which was rounded by heating, and glued to the end of a 2-0 monofilament nylon suture 40 cm in length. The tip of the occluding device was introduced into the left extracranial internal carotid artery through a polyethylene tube sheath inserted and fixed into the left common carotid artery. Catheters were inserted into the right femoral artery and vein for continuous arterial pressure measurement, blood sampling, and drug administration. An additional polyethylene tube was inserted into the abdominal cavity for administration of glucose solution. Following completion of surgery, halothane was discontinued, and an i.v. infusion of propofol was begun. Rats were fixed in an acryl cradle in the supine position and placed in the NMR device. The animals were assigned to one of two experimental groups. In one group (high-dose group, n=5), the infusion rate of 1% propofol was 2 ml h^{-1} (~60 mg kg^{-1} h^{-1}). In the second group (low-dose group, n=5), the infusion rate of 0.2% propofol, which was adjusted using normal saline to administer a similar fluid volume as that of the high-dose group, was 2 ml h^{-1} (~12 mg kg^{-1} h^{-1}). The intrarectal temperature was maintained at 37.5 (0.3)°C with a heating pad during the experimental period.

NMR measurements

A 2.0 T CSI Omega System equipped with an actively shielded gradient coil, Acustar S-150 (Bruker, Fermont, CA), was used in this study. A solenoid-type volume coil, 70 mm in diameter for transmission, and a surface coil 22 mm in diameter for signal detection was combined perpendicularly.

Brain lactate and *N*-acetylaspartate (NAA) were detected using the ^{1}H echo planar spectroscopic imaging (EPSI). The pulse sequence used in this study was described previously.[6 15] Measurements were acquired with 2 s repetition time (TR), 136 ms echo time (TE), 160 ms inversion time, 40 mm^2 field of view (FOV), 6 mm slice thickness at the centre of the brain, 4 k block size (16 points×256 echoes), 32 kHz spectral width, and 20 acquisitions for 10 phase encoding steps. The total acquisition time of one dataset of EPSI was 7.5 min. The EPSI data were Fourier transformed after zero filling, two 512×32×32 spectral datasets were obtained and added, and the metabolite images were constructed with 32×32 matrices.

Oedema was detected using diffusion-weighted echo planar imaging (EPI). The EPI was acquired with 3 s TR, 80 ms TE, 40 mm^2 FOV, 128×128 resolution, 3 mm slice thickness at the centre of the brain in the axial plane, and acquisitions. Diffusion gradients of 1290 and 2180 s mm^{-2} b values were applied separately on each X, Y and Z axis The total acquisition time of one dataset of diffusion-weighted EPI was 2.5 min. Processing of NMR data was performed as described previously.[6] Briefly, two diffusion trace images with 1290 and 2180 s mm^{-2} b values were constructed by averaging the three diffusion-weighted EPIs with the X, Y, and Z axis gradients.[16] From these two trace images and the EPI without diffusion gradient, the average diffusion coefficient (Dav) was calculated pixel-by-pixel, and the Dav map was constructed. As the Dav values decrease along with the oedema formation, it is considered that the lower the values, the more severe the oedema.[16 17]

Experimental procedure

The experimental procedure is shown in Figure 1. Briefly, 30 min after starting propofol infusion, baseline measurements of the arterial blood gas parameters and blood glucose concentrations were performed. One dataset of diffusion-weighted EPI and EPSI at the baseline was then acquired. Pre-ischaemic hyperglycaemia was induced by i p. injection of 20% glucose solution (2 g kg^{-1} glucose). Thirty minutes after glucose injection, arterial blood gas parameters and blood glucose concentrations were measured and MCAO on the left side was accomplished by advancing the tip of the occluding device into the middle cerebral artery. Immediately, diffusion-weighted EPI and EPSI were acquired alternately and repeatedly with a 10 min cycle. Sixty minutes after MCAO, reperfusion was induced by withdrawing the occluder to the extracranial internal carotid artery. Data acquisition was continued and repeated for the subsequent 120 min reperfusion period.

Statistical analysis

Values are expressed as the mean (SD). Repeated measures analysis of variance followed by the Bonferroni test were used for the comparison within group and between groups. A P value <0.05 was considered significant.

Results

Physiological data

Physiological parameters for each group are summarized in Table 1. In both groups, blood glucose concentration at the onset of ischaemia was elevated following injection of

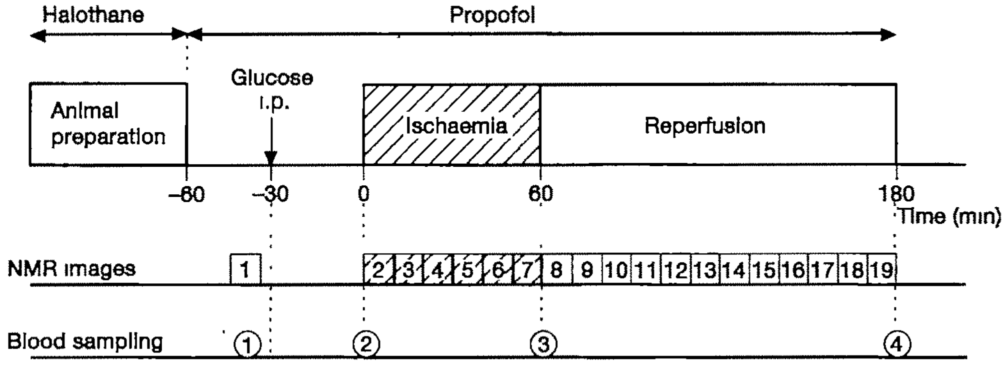

Fig 1 Experimental procedure for the NMR measurements. Arterial pressure measurement and blood sampling were performed before glucose injection, at the onset of ischaemia, at the onset of reperfusion and 120 min after reperfusion. The NMR images were obtained once before glucose injection, six times during ischaemia and 12 times after reperfusion.

Table 1 Physiological values for the two groups. Values are mean (SD) (n=5 in each group), $^*P$<0 05 compared with baseline within each group

	High dose	Low dose
Baseline		
Mean arterial pressure (mm Hg)	124 (15)	125 (24)
Blood glucose (mg dl^{-1})	108 (18)	108 (20)
Arterial pH	7 37 (0 02)	7 36 (0 07)
Pa_{CO_2} (mm Hg)	44 4 (3 5)	44 1 (3 0)
Pa_{O_2} (mm Hg)	233 (19)	214 (20)
Onset of ischaemia		
Mean arterial pressure (mm Hg)	140 (13)	130 (15)
Blood glucose (mg dl^{-1})	249 (20)*	255 (24)*
Arterial pH	7.35 (0 03)	7.34 (0 03)
Pa_{CO} (mm Hg)	42.0 (4.7)	42 0 (4.4)
Pa_{O_2} (mm Hg)	221 (25)	235 (17)
Onset of reperfusion		
Mean arterial pressure (mm Hg)	112 (13)	132 (11)
Blood glucose (mg dl^{-1})	98 (15)	112 (17)
Arterial pH	7 34 (0 03)	7 34 (0 02)
Pa_{CO_2} (mm Hg)	44.7 (2 7)	41 5 (4 7)
Pa_{O_2} (mm Hg)	216 (25)	231 (24)
120 min after reperfusion		
Mean arterial pressure (mm Hg)	80 (18)*	118 (29)
Blood glucose (mg dl^{-1})	70 (5)*	73 (11)*
Arterial pH	7.40 (0 03)	7 39 (0 05)
Pa_{CO_2} (mm Hg)	44 0 (4 3)	43 1 (2 3)
Pa_{O_2} (mm Hg)	201 (25)	218 (38)

glucose but this concentration decreased below baseline 120 min after reperfusion in both the high-dose propofol and the low-dose propofol groups. Mean arterial pressure 120 min after reperfusion in the high-dose propofol group was significantly lower than baseline. There were no significant differences in arterial blood gas parameters and blood glucose concentrations between the groups at all sampling points. Mean arterial pressure 120 min after reperfusion in the high-dose propofol group was lower than that in the low-dose propofol group, but the difference was not significant.

Lactate accumulation

Images of lactate accumulation are shown in Figure 2A. After the onset of ischaemia, lactate accumulation was detected in the ischaemic region both in the high-dose propofol group and the low-dose propofol group. After reperfusion, the lactate accumulation disappeared gradually

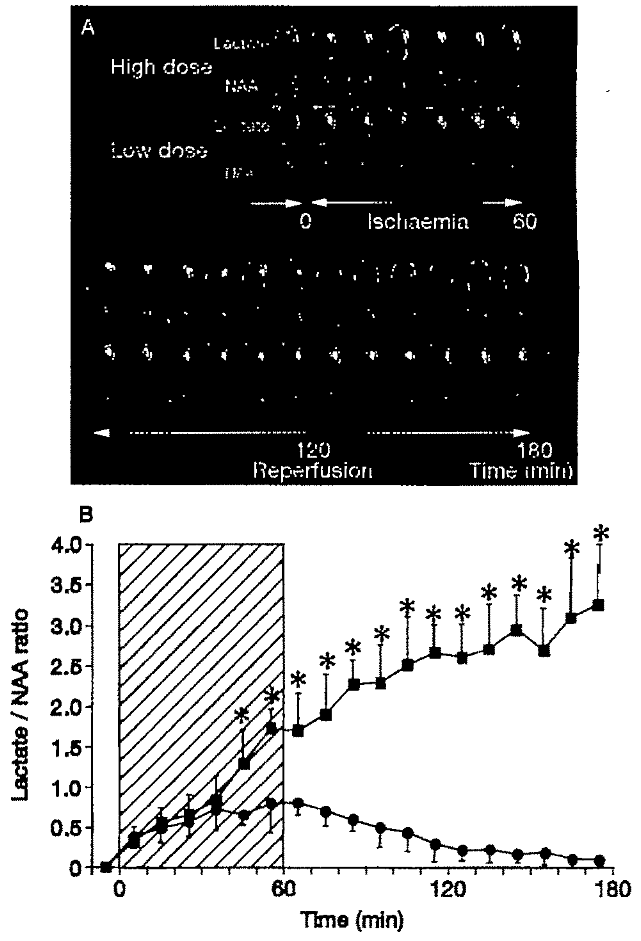

Fig 2 Effects of propofol on lactate accumulation. (A) Representative lactate and NAA images. (B) Changes in lactate/NAA ratio in the ischaemic region of the high-dose (●) and low-dose (■) propofol groups. The hatched area represents ischaemic period. Values are mean (SD) (n=5 in each group). Asterisks denote significant difference between the high-dose and low-dose propofol groups at the same time points ($^*P$<0 05)

in the high-dose propofol group, while it did not decline in the low-dose group. To evaluate the lactate accumulation quantitatively, the lactate/NAA ratio was calculated from the spectra extracted from the ischaemic region. As NAA is distributed through the brain in neurons but not in glia, it can be used as a marker of neuronal density.[18] As shown in Figure 2B, the lactate/NAA ratio increased from the onset of ischaemia until 40 min after ischaemia similarly in both groups. However, in the high-dose propofol group, no further increase was observed and the ratio decreased gradually to the baseline concentration after reperfusion. In the low-dose propofol group, the ratio increased continuously during ischaemia and reperfusion.

Oedema formation

Images of the oedema formation are shown in Figure 3A. Oedema gradually appeared in the ischaemic hemisphere after the onset of ischaemia both in the high-dose and low-dose propofol groups. However, during reperfusion, oedema disappeared in the high-dose propofol group, whereas it did not decline in the low-dose propofol group. To evaluate oedema size quantitatively, the number of pixels with an average diffusion coefficient (Dav) below 0.6×10^{-3} $mm^2\ s^{-1}$, which can be considered as the formation of oedema,[6] was counted from the left hemisphere. During ischaemia, the pixel number increased to a similar extent in both groups. After reperfusion, the pixel number in the high-dose propofol group decreased and returned to the baseline level, whereas that in the low-dose propofol group continued to increase (Fig. 3B).

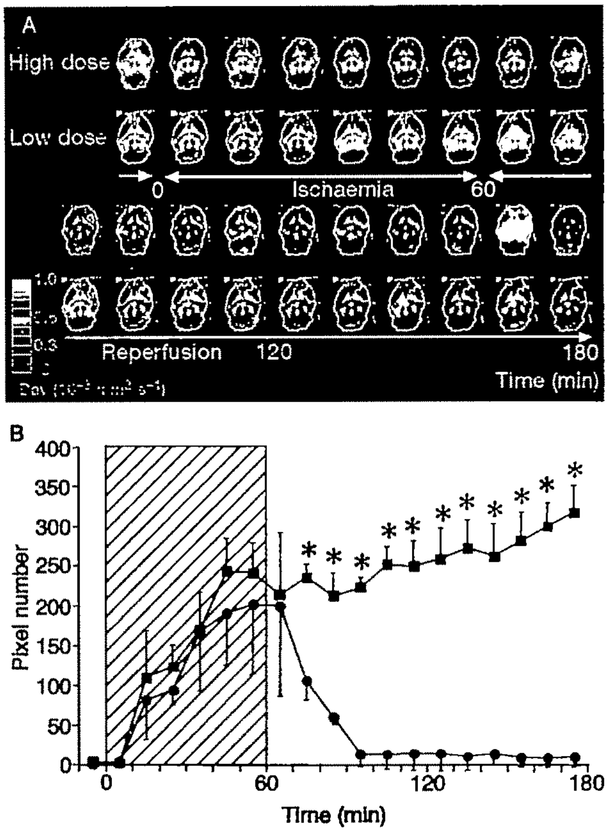

Fig 3 Effects of propofol on oedema formation (A) Representative average diffusion coefficient (Dav) maps Dav values below 0.6×10^{-3} $mm^2\ s^{-1}$ are shown with colours, which means oedema formation (B) Changes in pixel number with Dav values below 0.6×10^{-3} $mm^2\ s^{-1}$ of the high-dose (●) and low-dose (■) propofol groups The hatched area represents ischaemic period Values are mean (SD) ($n=5$ in each group) Asterisks denote significant difference between the high-dose and low-dose propofol groups at the same time points ($*P<0.05$)

Discussion

In the present investigation, the NMR study revealed that high-dose administration of propofol attenuated the accumulation of lactate and the formation of oedema in the ischaemic region in hyperglycaemic rats.

We used SHRs for the MCAO model, because the MCAO-induced infarction in SHRs is larger in volume and more reproducible than that in other strains of rats.[19] I.p. injection of glucose produced higher blood glucose levels than controls at the onset of ischaemia, but this was lower than controls 120 min after reperfusion. In studies using diabetic rats, it was reported that the severity of the brain ischaemia depended not on the duration of hyperglycaemia, but on the blood glucose level at the onset of the ischaemia.[20 21] Therefore, the time course of the blood glucose changes in the present study can be considered sufficient to aggravate neuronal damage induced by brain ischaemia.

Ischaemia, as well as hypoxia, causes inhibition of aerobic metabolism, leading to production and accumulation of lactate, which induces tissue acidosis and cellular damage.[4 22] Hyperglycaemia-induced elevation of brain glucose concentration should accelerate lactate accumulation and aggravate ischaemia-induced neuronal damage.[5]

Propofol has been already shown to exert neuroprotective effects in cerebral ischaemia in normoglycaemic rats;[8–10] however, it has not been shown whether propofol can prevent ischaemia exacerbated by hyperglycaemia. Propofol has been shown to have profound depressive effects on cerebral glucose metabolism in rats and humans.[11 12] In rats, propofol inhibited the cerebral glucose utilization in a dose-dependent manner.[12] Therefore, in the present study, we suggest that high-dose propofol suppresses glucose metabolism more profoundly than low-dose propofol, which lowered lactate accumulation in response to ischaemia.

Reactive oxygen intermediates have been implicated in the pathophysiology of ischaemia-induced brain damage.[23 24] Hyperglycaemia accentuates acidosis in the ischaemic region, which enhances formation of hydroxyl radicals, resulting in the exacerbation of ischaemia-induced brain damage.[25 26] The chemical structure of propofol resembles that of α-tocopherol, an antioxidant.[27] Indeed, the antioxidant properties of propofol have been reported.[28,29] Therefore, the neuroprotective effect of propofol in hyperglycaemic rats may be partially attributable to its antioxidative properties.

In the present study, neuroprotective effects were observed with a relatively high-dose of propofol (60 mg kg^{-1} h^{-1}). This propofol dose roughly corresponds to that which produced burst suppression on electroencephalograms in rats.[8,9] In humans, 15–30 mg kg^{-1} h^{-1} of propofol was reported to give rise to burst suppression in electroencephalograms.[30] Therefore, the findings of the present study suggest that 15–30 mg kg^{-1} h^{-1} of propofol may be neuroprotective in brain ischaemia in diabetic patients. However, further studies will be required to clarify the neuroprotective effects in humans.

In conclusion, high-dose propofol attenuated lactate accumulation and oedema formation in cerebral ischaemia in hyperglycaemic rats. As lactate accumulation is considered to exacerbate brain damage, the use of propofol during neurosurgical operations may be beneficial to prevent neuronal damage especially in diabetic patients.

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BJA

REVIEW ARTICLE

The role of non-technical skills in anaesthesia: a review of current literature

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The complexity of patient care in the modern operating environment demands a wide range of skills and attributes from anaesthetists. Conventional training has placed great emphasis on acquisition of the necessary knowledge and practical skills to ensure competent practice. However, satisfactory patient outcomes will only be realized if appropriate plans can be executed effectively. This requires a particular set of skills, such as communication, team-working, planning, resource management and decision-making, that are used integrally with medical knowledge and clinical techniques. Such skills are not new in anaesthesia; good anaesthetists have always demonstrated these competencies but they have not featured explicitly in formal anaesthetic training programmes. These skills are sometimes referred to under the general heading of 'human factors', but more specifically, as they do not relate directly to the use of medical expertise, drugs and equipment (i.e. clinical knowledge and technical skills), they can be described as non-technical skills. Non-technical skills can be divided into two subgroups: (i) cognitive or mental skills (e.g. decision making, planning, situation awareness) and (ii) social or interpersonal skills (e.g. team-working, communication, leadership). Both groups of skills are necessary for safe and effective performance in the operating theatre environment.

From an industrial psychologist's perspective, anaesthesia has much in common with the aviation, air traffic control and nuclear power generation industries. All of these high-reliability domains share safety as a prime goal and they rely on having well-designed workplaces, equipment and systems, as well as safety-focused organizational climates. Personnel must be suitably skilled to ensure they can deal with the demands of their complex work environments. This usually involves maintaining awareness of dynamic situations involving multiple players and being able to deal with critical events in stressful, time-pressured situations characterized by ill-structured problems, shifting goals and incomplete feedback. If problems do arise in these circumstances, the limitations of human performance, combined with latent errors in the system, can potentially lead to adverse safety outcomes. In recognition of this, the other high-reliability domains have introduced special training programmes to raise awareness of problems arising from human factors and to support the development of non-technical skills.[42] There is considerable opportunity for the cross-feeding of ideas from different domains, particularly aviation, with which anaesthesia has most often been compared.[10 18] However, while there is a wealth of information on non-technical skills from psychological research in other work-places, the issues may not extrapolate directly and so it is important that these skills are defined carefully within the context of anaesthesia. The aim of the present paper is to review the relevant human factors literature in anaesthesia in an attempt to delineate the role of non-technical skills in anaesthetists' practice. The material is presented in four sections that are in line with the main data sources that would normally be used to identify critical behaviours: (i) incident reporting; (ii) observational studies from the real world and simulators; (iii) attitude questionnaires; and (iv) theoretical models. The final section summarizes key issues for training and assessment and discusses the limitations of current data sources that could be used to identify the non-technical skills of anaesthetists.

Incident reporting

One of the most common sources of data for revealing critical behaviours is incident reports. These take the form

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of mandatory occurrence reports, detailed accident investigations, company incident reports and confidential human factors reporting systems. They can be analysed to reveal the underlying causes of the event and systemic deficiencies. Different report formats produce different types of data: some provide free text descriptions of events explaining what happened, what led up to the event, who was involved, etc., while others use more structured classifications to obtain details of technical and non-technical factors.[25] Incident reports have been a major source of information in the development of non-technical skills training in aviation, and they continue to be used to 'close the loop' when designing system improvements. In anaesthesia, data from incident reporting schemes have been available for 20 yr. Indeed, it was the realization that human error is implicated in as many as 80% of anaesthetic incidents[7 27 44] (a figure comparable to findings in other industries) that prompted much of the subsequent human factors research in the field.

However, when the data from these medical incident reporting systems are scrutinized, they provide only limited insight into non-technical skills. Although many of the studies in anaesthesia have looked to the psychological literature for advice on how to analyse incidents,[1] the available human error classification systems do not appear to be used extensively to identify the underlying behavioural causes of the incidents. Analysis tends to occur at a more operational level, so that each incident has a descriptor of what happened (e.g. wrong drug administered) and a contributory factor (e.g. distraction) that helps to explain what led to the event. Unfortunately for the purposes of understanding the role of non-technical skills in anaesthesia, these technically oriented systems do not really provide the finer-grained level of information necessary to understand where the skills broke down.[9] Furthermore, the use of human factors codes is limited (but see Runciman and colleagues[41]) and they are not clearly defined on reporting forms. In addition, under-reporting may affect the quantity and quality of the human factors data provided. This may be due to ambiguity in the definition of what constitutes an incident, confusion over the classification codes provided, time availability, concern over legal or disciplinary action, and a professional culture with unrealistically high expectations of human performance under stress and fatigue.[21 43] These difficulties aside, there have been several studies describing classifications of anaesthesia incidents. Some examples and the types of non-technical skills they highlight are discussed below.

In the first study of its type, Cooper and colleagues[7] at Harvard investigated outcomes other than death in a retrospective study in which anaesthetists were asked to describe preventable incidents that they had observed or participated in, involving either a human error or equipment malfunction. In addition, the anaesthetists were asked to describe factors that had been causal in the event. They coded 359 incidents using a specially developed branching classification scheme. The results showed that 82% of the incidents involved human error whereas only 14% involved equipment failure. The descriptions of the events do not really give much insight into non-technical skills, but this information can be found as associated factors, which include poor communication with the team, laboratory etc., inattention/carelessness, haste, fatigue, distraction and insufficient preparation.

A second, wider study[6] by the same group confirmed many of their earlier findings. Additional causal factors detected in this sample included excessive dependency on other personnel, failure to follow personal routine and failure to follow institutional practice. The incidents were categorized into four main types: technical, judgemental, monitoring/vigilance, and other types. Both judgemental and monitoring/vigilance could be considered as human error categories. The latter are clearly linked to non-technical behaviours, although for the judgemental category it is difficult to determine the underlying causes because of the lack of information about why or at what stage the judgement failed.

In another key study, the Australian Incident Monitoring System (AIMS)[41] collected data on a comprehensive anonymous incident form that provided a large number of categories under main headings covering what happened, why it happened, the anaesthesia and procedure, where and when it happened, patient outcome, and to whom it happened. Williamson and colleagues[44] examined the human factors that either contributed to or helped minimize the incidents and suggested corrective strategies. Following Reason's work,[39 40] they described errors as knowledge-based, rule-based, skill-based, technical or system-based. The first four categories were classified as human failures and were found in 83% of reports. The most common contributing factors included error of judgement, failure to check equipment, fault of technique, other equipment problem, inattention, haste, inexperience, and communication problems.

It is clear just from the studies of these two databases that a number of common errors that arise, e.g. inadvertent drug swaps, failure in communication, insufficient monitoring, are not related primarily to clinical knowledge or technical skills but rather to other non-technical problems. While these investigations have highlighted the types of errors that occur in anaesthesia and their associated factors, most do not provide a detailed analysis of causality and the error mechanisms leading to the incidents or recovery from them. For example, 'emergency situation' has been cited as an associated factor but it is not clear what it is about the emergency that causes the problem or what other factors are associated with this. There are some exceptions, such as the AIMS study[41] and the work of Nyssen,[35] who investigated risks associated with failures in decision functions. Even here there is still no real explanation of the linkages between factors and descriptions of the factors (e.g. the sort of communication problem involved, and the question of which errors are associated with which type of knowledge). It may be that this sort of information cannot be identified from incident reports as they currently exist, and so other types of investigation are needed to uncover the behaviours that break down in error situations and the skills that aid recovery. Or, to allow comprehensive understanding of the role of non-technical skills, more advanced techniques may need to be applied to the analysis of anaesthesia-critical incidents, such as the root-cause analysis being used by Busse and Johnson[3] to identify the proximal and distal factors in ICU events. Accepting the current limitations on the information available from incident-reporting systems in anaesthesia, the results of the studies reviewed indicate that deficiencies in non-technical skills contribute significantly to adverse outcomes. These incident studies provide some insight into the components of these skills, but further identification and understanding of the skills is restricted because of limitations in the human factors aspects of these coding schemes.

Observational studies in anaesthesia

Another important source of data to reveal the non-technical skills in anaesthesia is the observation of performance in both real and simulated environments. While incident reports only provide information about the things that went wrong, observational studies allow behaviour to be examined under all conditions, both in the real operating environment and in the simulator. This can provide information about what is going on when things go well, what prevents everyday difficulties from leading to more serious problems, how different groups of people perform differently, etc. The use of simulators also allows experimental trials to be undertaken so that anaesthetists' behaviours and resulting performance can be measured and compared under controlled conditions.

As sources of research information, both simulators and real operating theatre observations have limitations. Collecting data within the operating theatre or emergency room can be difficult as the events of interest may not occur, it may be difficult to observe the whole environment either directly or using video, the presence of a researcher may affect normal behaviour, and also because of issues of consent and confidentiality. It is easier to set things up for observation or video recording in the simulator environment, although clearly some aspects of simulator fidelity may affect performance.[29] Despite these limitations, both methods have been used to study anaesthetists' practice, and the findings can be examined for evidence of non-technical skills.

Real environment studies

One of the few observational studies that has examined non-technical skills during theatre operations was carried out by Helmreich and Schaefer.[22] They observed the performance of whole operating theatre teams in Basel and categorized the behaviours using an existing aviation team skills framework. Errors were identified that included failure to complete a checklist for the anaesthesia machine; consultant distracted from a decision on the patient by problem in another operating room; failure to discuss alternatives and to advocate a course of action; and failure to debrief actions during operation.[21] These findings are comparable with problems identified from incident reports and simulator research but provide additional insight into the real level of interaction between the anaesthetic and surgical teams. Problems observed with communication and coordination across this barrier are of particular concern as they affect the maintenance of a shared understanding of the situation.

To provide a more systematic approach to measuring team processes, Helmreich and colleagues[23] revised an aviation line operations audit checklist to produce a detailed form that allowed the operating room teams to be scored on a rating scale using team performance indicators. The team's technical and overall performance was also scored. The key components of the operating room checklist were divided into three main sections: team concerns; the decision-making process and communication; and management of the work situation. Data collected have indicated that 20–30% of observations of briefing and team formation showed behaviour that was unsatisfactory or met only minimal expectations; for the indicator on exchange of information on decisions, 20–40% of observations were below the set standard.[19] These results show that, while non-technical skills appear to have an important role, they are not always used. This can have consequences for overall clinical performance.

A major body of real life observational research has been conducted at the Shock Trauma Centre at the University of Maryland Medical Centre,[28–33 46–49] looking at the management of patients arriving in the emergency department by trauma teams, including anaesthetists. Data were collected using video cameras located in the admitting bays and an operating room. In the first study, Mackenzie and colleagues[31] used the video data to analyse group decision-making processes. They found that, under stressful, time-pressured situations, knowledge-based errors, such as incorrect drug administration or dosage, were observed. However, these contrasted with the anaesthetists' self-reports of primarily procedural-type errors, such as not preoxygenating the patient before intubation. This highlights one of the main problems associated with self-report: that people's accounts of their behaviour may not be related to what they actually do. The videos also showed that, while in periods of high time stress there was an increase in short cuts and task-shedding, and there was more verbal communication, particularly to convey strategies or delegate tasks. The authors point out that some of the problems associated with uncertainty, which was one of the stressors, could be reduced by increased monitoring and preparation.[31]

One particular area of interest in relation to cognitive skills was the occurrence of fixation errors.[5 13] Xiao and colleagues[49] observed fixation errors arising from the anaesthetists moving too fast, such that they rushed past certain cues and used other, improper information, and from moving too slowly and failing to update old plans and courses of action when necessary. These fixation errors were hypothesized to be 'partly the results of the interplay between the nature of complex environments and the strategies used by practitioners in dealing with complexity',[49] and to result in a loss of situation awareness (for descriptions of this construct see Endsley[8] or Gaba and colleagues[14]). Xiao and colleagues[48] investigated the dimensions of task complexity and their impact on crisis activities and team processes in the trauma room. They identified four components of task complexity which affected team coordination in different ways. Multiple, concurrent tasks led to goal conflict, task interference and competition for access to the patient. Uncertainty regarding the case led to differences in opinion when interpreting information and difficulties when trying to anticipate the actions of other team members. The use of contingency plans caused difficulty in knowing when to switch tasks and how then to reallocate activities. Finally, a high workload caused procedures to be compressed and this deviation from normal strategies further increased the complexity of the situation. To improve team coordination under these circumstances, Xiao and others[48] advocated training in explicit communication and developing work procedures that make 'certain verbalisations mandatory'.

The importance of communication was further highlighted by Xiao and Mackenzie,[46] who looked at both verbal and non-verbal task coordination. Four types of coordinating behaviour were observed: following protocol; following the leader; anticipation; and activity monitoring. When following protocols, e.g. Advanced Cardiac Life Support, all team members should know exactly what to do and what is expected, so that minimal verbal communication is required. By watching the leader, team members know what they should do and discern their instructions from the leader's activities. Similar, but based on observation of the patient's physiological status, is anticipation, e.g. a suction catheter being offered in response to a patient gagging, in anticipation of vomiting. However, problems could arise when relying on anticipation if team members interpret the situation differently. Activity monitoring describes behaviour in which one team member watches someone else complete their tasks in order to find out when they could begin the next activity. This was found to occur between the anaesthetic and surgical teams: the latter not necessarily announcing their plans to the anaesthetists. Again, this could cause problems, as it is possible to make the wrong inference about the situation from just observing other team members' activities. Information flow by explicit verbal communication was found to be relatively rare and was usually limited to sharing information about the situation and further plans only when the team had a decision to make.

Clearly,. problems can arise when so much is left unspoken. Xiao and Mackenzie[46] identified three situations when this coordination broke down: when there was pressure to seek alternative solutions; when it was necessary to initiate unexpected, non-routine procedures; and when there was a diffusion of responsibility after a change in plan and the team members had to adjust themselves to new tasks and roles. Overall, the most significant finding of this study is that it highlights the reliance of trauma teams on non-verbal cues rather than verbal communication for coordination. It would be interesting to see if these cognitive skills and task coordination strategies are used in the same way in normal elective operations and if the same difficulties arise if a crisis occurs in theatre.

Simulator studies

Understanding how the behaviour of experts differs from that of novices is an important means of understanding non-technical skills. Several groups have looked at the role of experience in the management of critical incidents, using the simulator to identify differences in behaviour. In the USA, Gaba and DeAnda[12] used a high-fidelity patient simulator to compare the performance of first- and second-year anaesthesia residents giving an anaesthetic during which a number of major and minor events occurred. Transcripts of the incidents were scored for factors that included time to detection, time to correction and the resolution strategy. Analysis showed that the time taken to correct the problem was related significantly to experience, the more experienced anaesthetists making a diagnosis and beginning treatment quicker. This suggests that experienced anaesthetists are better at identifying and making use of the relevant cues leading to better situation awareness and the generation of a more accurate mental model from which to recognize the appropriate problem solution. However, individual performance amongst the more experienced anaesthetists was variable and while many less experienced residents did act correctly, some with greater clinical experience did not. Drawing from findings in other areas, such as nuclear power plants, Gaba and DeAnda[12] speculated that response to acute intra-operative problems may be largely accomplished using precompiled procedures and that even inexperienced trainees can incorporate some of these procedures and retrieve them under appropriate situations. The fact that some of the less experienced residents would have had training in life-support protocols more recently may have accounted for instances when they performed as well as or better than the more experienced residents.

Byrne and Jones[4] investigated performance in four groups of anaesthetists with experience ranging from less than 1 yr to over 5 yr, using the low-fidelity ACCESS simulator. After a brief introduction to the simulator, participants were presented with a series of scenarios, which included problems that required interventions such as drug treatments and i.v. fluids. Times to problem recognition, treatment identification and implementation were used as measures of performance. Replicating the findings from earlier studies, speed of treatment was shown to be linked to experience, the least experienced group performing significantly worse than the other groups. However, even some very experienced participants handled the situations poorly and, regardless of years of experience, no one used relevant treatment guidelines in the scenarios for which they were available. When analysing the actual behaviours observed during the scenarios, the authors found that although trainees with less experience took longer to treat the problem, their more systematic approach to case management could actually be considered safer than the faster approaches adopted by those with more experience. Unfortunately, these results do not provide much insight into the decision processes and management strategies of anaesthetists with more experience or indeed how they might normally seek to avoid crisis situations before they occur.[4]

Nyssen and De Keyser[36] investigated problem-solving in novices (second and third years) and more experienced anaesthetic trainees (fourth and fifth years). Each participated in videotaped simulations of four problem scenarios that varied in complexity. Again, the results showed that, regardless of the complexity of the scenario, the more experienced anaesthetists took less time to diagnose the problem. Indeed, the majority of the novices were unable to make correct diagnoses for the two most complex scenarios. Perhaps of more interest for understanding performance were the descriptions of the different behaviours of the groups. The more experienced anaesthetists were more involved in regulating the anaesthetic (administering drugs, attending to airway and ventilation, monitoring), thus allowing them to maintain better situation awareness and anticipate future changes. While there was no overall difference in evaluation of the problem situations, the activities of the two groups did vary. The novices generated more hypotheses about the problem, whereas the more experienced group displayed more evidence of planning and set up treatment more efficiently. All of these results suggest that the more experienced group were better able to use the information provided to produce a diagnosis and hence begin treatment sooner. Moreover, if that diagnosis subsequently turned out to be incorrect they were better able to re-evaluate using other cues to produce a correct diagnosis. Thus, what appears to come with experience is the skill to focus on the important information and integrate this with existing knowledge of the situation to produce a solution. Knowing which factors to focus on allows the more experienced anaesthetists to prioritize tasks better and carry out activities flexibly.

While there are a number of methodological difficulties involved in collecting data in the real environment and in the simulator (such as the limited availability of validated performance measures), observations of anaesthetists' performance can provide a valuable source of information regarding their non-technical skills. The studies show in particular that verbal communication, individual and team situation awareness, problem recognition, decision-making and re-evaluation appear to be key skills.

Attitude questionnaires

The final source of data on non-technical skills comes from attitude measurement studies using questionnaire-based surveys. While not providing information on the skills themselves, they do give an insight into how they are perceived and valued by anaesthetists. One of the main uses of attitude questionnaires has been for course evaluation after simulator training. The results of such surveys are usually positive and are a good source of feedback on simulator courses (for an example see Holzman and colleagues[24]), but these data do not add much to our understanding of anaesthetists' non-technical skills.

Investigating attitudes towards production pressure amongst Californian anaesthetists, Gaba and colleagues[16] found that, while the majority of anaesthetists had good working relations with their surgeons, over half did not believe the surgeons understood the risks associated with anaesthesia. Indeed, almost half the respondents had observed an anaesthetist pressured into giving an anaesthetic in an unsafe situation. Again, while these data do not give us an indication of the specific non-technical skills being used by anaesthetists, they highlight the importance of considering social and organizational factors when investigating anaesthetist performance.

Helmreich and Schaefer[22] adapted a questionnaire that had been designed to survey pilots' attitudes towards leadership, team-working and safety issues to produce the Operating Room Management Attitudes Questionnaire (ORMAQ). Results from surveys of operating theatre teams in the USA and Switzerland showed anaesthetists agreeing that 'communications and coordination are as important as technical proficiency in the operating room'. They also disagreed with the statement 'team members should not question senior staff' and endorsed 'consultative management styles in the operating room', even though they encountered more autocratic styles in reality.[22] Attitudes towards the effects of stress and fatigue were of more concern,[21 43] many anaesthetists agreeing that their performance was unaffected by fatigue and that their decision-making was as good in an emergency as in normal situations. While this unrealistically high expectation of human performance has also been documented for airline pilots and surgeons, it does not encourage anaesthetists to accept error as a normal occurrence or to realize that critical incidents may occur because of stress or non-technical factors. A recent Scottish survey by Aberdeen University using the same questionnaire has found similar attitude patterns (R. Flin, G. Fletcher, P. McGeorge and A. Sutherland, in preparation).

Theoretical models

In spite of the difficulties in collecting information on anaesthetists' performance and the factors that influence it, there has been some valuable research conducted in this area, mainly in the USA. While there are many questions still to be answered, the literature reviewed above highlights a range of non-technical skills that are critical in supporting anaesthetists' performance. Several models describing anaesthetists' non-technical skills have now been developed on the basis of generic models of error mechanisms, decision-making, situation awareness, team performance and other human factors research. The models fall into two complementary categories, aligned with the focus of the underpinning research. First there are *cognitive models*, such as Gaba's process model of anaesthetists' decision-making/problem solving behaviour.[13] These models concentrate on the individual's mental processes. Secondly, there are *team models*, such as Helmreich's model of operating room performance,[22] which focus on team and organizational factors.

Cognitive models

On the basis of findings from simulator studies, incident reports and using cognitive psychology theories[38 40 45] as a framework, Gaba[11] developed a model to describe anaesthetists' decision-making processes. The initial model was based on what he called four levels of human information processing: (i) processing sensory data from the environment and controlling actions (sensorimotor level); (ii) following rules for solving problems (procedural level); (iii) solving problems through reasoning (abstract level); and (iv) coordinating attention and interactions (supervisory level). The model describes how anaesthetists become aware of a problem and how they would then act to resolve the situation. In later versions of this model, which incorporate ideas from aviation,[42] a resource management level has been added to produce 'a comprehensive model of dynamic decision making and crisis management'.[13] This final model is used as a framework for Gaba's simulator training programme in Anesthesia Crisis Resource Management (ACRM), which particularly emphasizes non-technical skills. The activities associated with each processing level are summarized in Table 1. Investigating performance in ACRM, Gaba and colleagues[15] conducted a set of studies using both technical and behavioural (or non-technical) assessments and found that crisis management scores were strongly correlated with leadership, communication and distribution of workload. However, there was more variability between raters' scores of anaesthetists' behavioural performance than for technical performance, highlighting the difficulties associated with identifying and measuring non-technical skills.

The first part of the model is the sensorimotor level. At this level the anaesthetist is engaged in basic observation and verification activities: checking the patient, monitoring the displays (heart rate, blood pressure, etc.), observing the activity of the surgical team, and combining these to maintain a good level of situation awareness. The anaesthetist then carries out separate actions to confirm and cross-check that the information is accurate and reliable. For example, if the non-invasive blood pressure monitor showed a low value that was not expected, the anaesthetist would confirm that the reading was accurate by checking the patient's pulse, repeating the measurement, noting any changes in monitored signals. Although closely linked to observation, this verification activity is considered to be a separate task, which if omitted may contribute to incidents occurring. The supervisory level of control allocates the mental resources for the task. The anaesthetist will determine whether he or she needs to pay particularly close attention to surgical activities, for example during certain activities such as insertion of laparoscopic trochars, or whether attention can also be widened to activities such as completing the anaesthetic record.

The next stage of the decision-making process occurs at the procedural level, where the anaesthetist uses the information collected about the patient to identify and anticipate problems. The first task is to assess the situation and decide what course of action is necessary. It may be that the only action necessary is to continue monitoring the situation. Or the cues that are detected may suggest a problem; this must be identified, its consequences for the patient anticipated and a solution selected. One of the difficulties Gaba and colleagues[13] associate with this activity is that there may be an absence of definitive cues for a specific problem, and so heuristics, or rules of thumb, may be used to assist in identifying the problem. Depending on the urgency of the problem and the familiarity of the situation, the model then divides activities into continuing on the procedural level or moving to the abstract level. In the former case, the anaesthetist is able to use precompiled responses, for example Advanced Life Support protocols or the experts' own preplanned strategies, to dictate a course of action. In cases where the problem is novel or the patient does not respond to an initial solution, the model moves into the abstract level, where the anaesthetist may have to return to basic principles of medical knowledge and use reasoning to identify the appropriate course of treatment. This reasoning activity is more time-consuming and would be less favoured in emergency situations. Gaba and colleagues[13] noted that this type of reasoning seemed to occur alongside the use of the precompiled responses, linking actions back to medical concepts, perhaps to cross-check on their validity.

The next stage in Gaba's model involves the implementation of the plan developed during the problem-solving

Table 1 Processing levels and activities described by Gaba's model of decision-making by anaesthetists[11 13 14]

Cognitive level (lowest to highest)	Mental activity	Activities
Sensorimotor level	Processing sensory data and managing routine tasks	Observation, verification, problem recognition and assessment. Routine physical activities such as drug administration
Procedural level	Solving problems by applying rules	Identify and solve problems by applying precompiled responses
Abstract level	Solving problems by reasoning	Uses mental resources to create mental model of problem and to work out solution from first principles
Supervisor level	Supervisory control	Allocates attention and mental resources
Resource management level	Resource management	Uses available resources, information, equipment and personnel to manage perioperative care of patient

stage. As this usually involves the execution of a physical task, such as administering drugs or adjusting the anaesthetic machine, this part of the model is included at the sensorimotor level. It is not described in detail other than to identify the types of errors that can occur, namely slips of action such as using the wrong syringe.

The supervisory control level is responsible for the coordination of tasks through allocation of attention. This determines how much time and how much attention is given to making observations, problem recognition, selecting a response and ensuring that actions are implemented. While it is not clear how much of this supervisory control is under conscious control and how much is automatic, particularly in experts, it is clear that this is a vital process and problems can result in overload and potential failure to execute important steps, such as re-evaluation. As with other parts of the model, situation awareness is an integral part of the supervisory control process.[14]

The highest level of processing in the model is that of resource management. At this level, the anaesthetist identifies and attempts to utilize all available resources. Activities necessary for leadership, monitoring and cross-checking and communication are all coordinated from this top level. All of the higher-level perioperative aspects of case management are controlled from here, as are interactions between the individual anaesthetist and the rest of the team. While it is not stated in descriptions of the model, it is assumed that this level of control is under conscious and deliberate control. It is also something that can hopefully be addressed by training, as this feature of anaesthetists' performance has been found to be lacking, particularly in crisis situations.

The Belgian researchers Nyssen and De Keyser[36] have identified a simple model of problem-solving that is similar to Gaba's phases of problem recognition, action and re-evaluation. This model shows two problem-solving strategies identified in novice and more experienced trainees, where cues and information are detected and hypotheses are tested against corrective action. On the basis of a re-evaluation of the situation, the diagnosis is verified and new hypotheses are identified if necessary. In the first strategy, when the initial corrective action does not seem to be correct, re-evaluation is based on the original cues that led to the incorrect diagnosis. Thus, new hypotheses must continue to be generated and tested while the situation is not resolved. Essentially, the anaesthetist is fixated on a limited set of cues and does not look for any alternative information. For example, concentrating on the patient's blood pressure recording but not using other information, such as the heart rate, end-tidal carbon dioxide concentration and state of the surgical field. In the second strategy, when the first diagnosis does not seem to be correct, the anaesthetist looks for other cues and, through the collection and integration of more detailed information, is able to make the correct diagnosis. The key components of the effective strategy (associated with greater experience) were identified as effective monitoring strategies, anticipation, flexible allocation of attention, a knowledge of different situations, and the need to re-evaluate after each intervention. Thus, the model highlights the need for anaesthetists to have good situation awareness, to know and understand which cues are important when assessing the situation, and to anticipate the outcome of events given the available data, and for planned intervention. These elements of problem-solving are again common to the models of decision-making identified in other work domains. This model is useful because it starts to identify where experience has an influence and so is able to suggest simulator training that might be used to facilitate the development of problem-solving skills.

In Finland, Klemola and Norros[26] developed a conceptual framework that addresses the specific features of anaesthetists' thought processes. They started from the assump-

Table 2 Summary of factors in Helmreich's model of operating room performance[19 22]

Inputs	Team performance function	Outcomes
Organizational factors	Interaction with colleagues	Team
Resources, organization and practices	Same specialty	Patient safety
Cultural issues	Different specialties	Team performance
Patient		
Team factors	Task type	Individual and organizational
Composition	Case management	Attitudes
Familiarity	Technical	Job satisfaction
Group and intergroup norms	Cognitive	Personal development
	Social/interpersonal	
Individual factors		
Attitudes, personality and motivation		
Knowledge and training		
Stress and fatigue		

tion that the way anaesthetists perceive their patients will affect their behaviour. Using interviews, asking about the anaesthetist's various tasks and decisions, use of monitors and equipment, and means for dealing with uncertainty, they identified two types of orientation taken to the patient. The 'realistic orientation', described anaesthetists who focused on the uniqueness of each individual patient, communicating with them as being involved in a joint process, and recognizing the uncertainty present in the anaesthetic process. The 'objectivistic orientation' described anaesthetists who had an authoritative relationship with the patient, viewed the patient in terms of their disease and who did not recognize or acknowledge the uncertainty in the anaesthetic process. The latter type of orientation towards patients was found to be more common in their sample.

In a subsequent study, Norros and Klemola[34] also identified differences in the way the anaesthetists used the information available to them. One group of anaesthetists was found to use situational information only to confirm that the anaesthetic was running according to plan and responded on the basis of the type of patient and surgery. This 'habit of action' was described as 'reactive', and success was based on keeping the course of the anaesthetic on plan. A second group of anaesthetists was found to use situational information from a variety of different sources to build up an understanding of how the patient might respond. Thus, the anaesthetic plan was used only as a baseline from which to develop a fuller understanding of the patient as more information about the situation became available. This was described as an 'interpretative' habit of action. Perhaps not surprisingly, the reactive habit of action was associated with an objectivistic orientation towards the patient and the interpretative habit of action was associated with a realistic orientation.

What all these models have in common is a focus on the cognitive processes associated with the anaesthetist's tasks, particularly those necessary for dealing with multiple data sources, uncertainty about the patient and sometimes limited resources. Most of them, with the exception of the framework of Klemola and Norros[26] (which in effect describes the need for good situational assessment), have been derived from more generic human information processing models. However, it is important that the particular social and environmental context of the anaesthetic task is taken into consideration, such as interactions with team members, limitations imposed by the layout of the workspace, and the organizational culture of the medical system. It is also essential that the current models continue to be enhanced and evaluated in line with growing understanding, and experience from other high-reliability industries which face similar types of safety challenges.

Team models

Helmreich and Schaefer[22] have proposed a model of operating room performance that takes as its focus the whole operating team rather than an individual anaesthetist's mental processes. It is based on a simple framework previously used to describe teamwork on flight decks[20] and was adapted for medical teams as a result of observations of theatre staff in Switzerland and the USA. The main components of the model consist of team input factors, team performance function, team outcomes and individual and organizational outcomes, in a feedback loop. These are summarized in Table 2.

The first part of the model relates to the team input factors. These are divided into organizational factors, team factors and individual factors, all of which have been found to affect team performance. Organizational factors are those that could be considered to produce system errors. The following are all examples of organizational factors. How the anaesthetics department and operating theatre suites are organized and how efficiently they run and communicate with each other will affect the availability of resources and the motivation with which people will work. Conflict between groups within the operating theatre can cause particular problems, as noted previously regarding anaesthetic and surgical teams. Different groups in the operating room may have different work norms and the pace of their work may vary. Cultural issues come into play here at professional, organizational and national levels. This is why it is very important to take care when generalizing from research from other countries with regard to UK hospitals. As these input factors affect overall team performance, different attitudes and expectations about roles and activities as a result of cultural norms could have an effect on performance. Finally, the performance of the team will be affected by the task demands, i.e. patient factors, including the type of surgery, which Helmreich and Schaefer[22] include as an organizational factor.

Helmreich and Schaefer[22] identify a number of team input factors, including the composition of the team. They note that the usual mix seems to be separate medical and nursing groups for both surgery and anaesthesia (their writing suggests that the nursing staff groups are fixed, whereas in the UK the nursing staff usually do not belong to either discipline specifically). Given that there are several distinct groups making up the team, the model suggests that group and intergroup norms need to be considered. For example, difficulties may arise because different parts of the team may expect different types of communication. Not mentioned, but clearly important, is the familiarity of the team. Groups that work together regularly may have more (or less) understanding of the group's expectations, capabilities and ways of practice.

Finally, individual factors include the attitudes, aptitudes, personality and motivation, knowledge and training, emotional state, and level of physical condition and fatigue. Therefore, the team may be more or less effective if members are tired and stressed or have less training or experience. Unfortunately, results from the ORMAQ survey[21 43] suggest that medical teams are very poor at acknowledging this fact. Together, organizational, team and individual factors combine to form the team's input for a procedure.

Team performance functions are divided into two types. The first describes the interaction either with colleagues from the same specialization (e.g. anaesthetists) or between specializations (e.g. anaesthetists and surgeons). The second describes the different types of tasks: cognitive and interpersonal issues, and technical aspects and case management. This is essentially a division into non-technical and technical tasks. Breaking the non-technical tasks down further, they describe activities involved in forming and maintaining the team, including leadership; those of communication and decision-making, including maintaining shared situation awareness and option generation; and those for maintaining workload and managing situation awareness through monitoring. The focus of this model is more on the identification of these factors and how they are maintained rather than complex descriptions of their construction. For a more detailed description of the processes at play in this central part of Helmreich and Schaefer's model, one can refer back to the cognitive models described previously.

The final component of the model relates to outcomes. Here, Helmreich and Davies[19] highlight the multiple outcomes of operating room performance. The most obvious is the patient's safety, but equally important for team performance are individuals' job outcomes. Helmreich and Schaefer believe that 'team processes that are perceived by participants as having been effective in maintaining patient safety should impact on morale and job satisfaction favorably'[22] and are likely to be used as feedback to the input and process stages of the model. It is at this stage in the model that debriefing and discussion of reported incidents can be used to support performance. In their final discussion of the model, the authors discuss how organizational interventions can be used to support team performance through training and safety reporting systems.

In common with their applied research programme, Helmreich's model considers anaesthetists' performance only as part of the wider team and the external factors that could influence it. This is very important, as the anaesthetist does not work independently of others, and the cognitive processes of the type described by Gaba and colleagues[13] should not only function at the individual level. Xiao and Mackenzie[46 47] also observed that organizational factors played a significant role in increasing uncertainty and task complexity. The description of Helmreich's team model is less detailed than that of the earlier cognitive models, mainly because the concepts are not described in such great depth. Factors relating to team function and management, decision processes and situational awareness are described but the underlying processes are not discussed as this is not the focus of their research. Therefore, to obtain a full understanding of the anaesthetists' performance it is necessary to integrate the two types (cognitive and team) to produce a single model. This should encompass a higher-level component describing interactions with the external environment and team process factors, as well as a lower-level component describing individual cognitive activities and task process factors. The model can be used to analyse incidents in terms of active failures (human errors) and latent conditions (safety of organizational systems)[39] and to ensure that all necessary skill areas are addressed in training programmes. The development of a taxonomy of anaesthetist non-technical skills will help provide a framework for further development of such a model.

Concluding remarks

What is clear from this review is that non-technical skills play a central role in good anaesthetic practice and that a wide range of behaviours are important. These include: monitoring, allocation of attention, planning and preparation, situation awareness, prioritization, applying predefined strategies/protocols, flexibility in decision-making, communication, and team-working. However, it is apparent that these skills and their roles are not discussed in the literature at an appropriate level of specification to allow complete understanding to be achieved. For example, prioritization is an elemental skill that is difficult to subdivide further, whereas team-working is a general category that requires further decomposition into its component element skills. It is at the more detailed element level that a taxonomy of such skills becomes useful for training and research[2 9 37], as it is then that the full range of skills and their roles can be investigated and the factors that influence them identified. While the purpose of this paper has been to review the role of non-technical skills in anaesthesia, this is only possible to a certain degree because of the limited definition of these skills in the literature. Thus, the research reviewed here highlights the main types of non-technical skills important in anaesthesia and describes some aspects of their role—how they are used and the consequences of non-use. But it is not possible from the extant literature to provide a full list of non-technical skills and their function, as each study tends to highlight a specific aspect of anaesthetists' performance rather than providing a comprehensive skills analysis. It is also worth noting that the majority of existing research has occurred outside the UK and, given the comments in the previous sections on the potential impact of cultural differences, it is important that more research is conducted in the UK.

Nevertheless, this review clearly shows that non-technical skills have a considerable influence on anaesthetists' performance and hence on patient safety. Therefore, there is a strong requirement to provide training at the knowledge and skills level that will teach and reinforce safe behaviours and attitudes. As a corollary, there is a need for more research to specify the key non-technical skills and to develop measures for assessing this component of anaesthetists' performance.

Indeed, one of the most important lessons learned from research in aviation is that, to maximize the understanding of non-technical skills, appropriate performance measures are essential.[42] Once available, these would allow the possibility of more systematic and empirical investigations into anaesthetists' non-technical skills and would provide a structured assessment tool that could be used in education and training (for a discussion of current observational assessment in anaesthesia, see Greaves and Grant[19]). One way to do this is to follow the example of aviation and supplement the limited data from the existing literature by using training needs analysis techniques, such as observations, interviews, surveys and reviews of incident reports, for the specific purpose of identifying the non-technical skills needed to underpin good practice in anaesthesia. From this, a behavioural marker system for anaesthetists' non-technical skills could be developed. Behavioural markers provide observable exemplars of good and poor behaviour for each element of a skill. The process of using behavioural markers is more objective than unguided forms of expert assessment, as the marker systems can be tested for reliability and validity. Inter-rater reliability is particularly important, and the observers making the assessments must be trained to ensure they are properly calibrated to use the measurement tool. A research project at the University of Aberdeen and the Scottish Clinical Simulation Centre, funded by the Scottish Council for Postgraduate Medical and Dental Education, is currently conducting a training needs analysis to develop such a behavioural marker system for use in the training of anaesthetists[8a] and other similar initiatives are also taking place elsewhere in Europe.

As Gaba says in a recent comparison of the health care system with other high-hazard industries, 'the issue of patient safety is no longer a hidden epidemic'.[10] Indeed, it is of increasing concern and efforts are starting to be made to resolve this at both the organizational and the specialty level. Considerable challenges remain for the profession, including a need to rapidly enhance our understanding of the role of non-technical skills in anaesthesia and their impact on patient safety.

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SHORT COMMUNICATION

Effects of remifentanil and alfentanil on the cardiovascular responses to induction of anaesthesia and tracheal intubation in the elderly

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Background. We compared the effects of remifentanil and alfentanil on arterial pressure and heart rate at induction of anaesthesia and tracheal intubation in 40 ASA I–III patients aged greater than 65 yr, in a randomized double-blind study.

Methods. Patients received either remifentanil 0.5 $\mu g\ kg^{-1}$ over 30 s, followed by an infusion of 0.1 $\mu g\ kg\ min^{-1}$ (group R) or alfentanil 10 $\mu g\ kg^{-1}$ over 30 s, followed by an infusion of saline (group A). Anaesthesia was then induced with propofol, rocuronium, and 1% isoflurane with 66% nitrous oxide in oxygen.

Results. Systolic arterial pressure (SAP) and mean arterial pressure (MAP) decreased after the induction of anaesthesia ($P<0.05$) and increased for 3 min after intubation in both groups ($P<0.05$), but remained below baseline values throughout. Heart rate remained stable after induction of anaesthesia but increased significantly from baseline after intubation for 1 and 4 min in groups R and A, respectively ($P<0.05$). There were no significant between-group differences in SAP, MAP, and heart rate. Diastolic pressure was significantly higher in group A than group R at 4 and 5 min after intubation ($P<0.05$). Hypotension (SAP <100 mm Hg) occurred in four patients in group R and three patients in group A.

Conclusions. Remifentanil and alfentanil similarly attenuate the pressor response to laryngoscopy and intubation, but the incidence of hypotension confirms that both drugs should be used with caution in elderly patients.

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Keywords: age factors, cardiovascular responses; analgesics opioid, remifentanil; analgesics opoid, alfentanil; intubation tracheal, responses; heart, heart rate; arterial pressure

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The cardiovascular responses to laryngoscopy and tracheal intubation have been well documented, and a number of methods may be used to modify them, including alfentanil and remifentanil.[1 2] The elderly, who comprise an increasing proportion of patients presenting for surgery, have a diminished physiological reserve, alterations in autonomic function, an increased incidence of coexisting cardiovascular disease,[3] and increased sensitivity to opioids and anaesthetic drugs.[4 5] These factors may combine to increase cardiovascular lability during induction of anaesthesia, with the attendant risks of myocardial ischaemia, stroke, cardiac arrhythmias, or sudden death.[6]

Few studies of the haemodynamic responses to intubation have been performed in the elderly, and none have used remifentanil. The aim of this study was to compare the effects of remifentanil and alfentanil in modifying the haemodynamic response to intubation in elderly patients.

Methods and results

With hospital ethics committee approval and informed consent, we recruited 40 normotensive, non-premedicated ASA I–III patients aged 65–85 yr undergoing elective

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surgery and requiring tracheal intubation. Exclusions were: concurrent vasoactive medication, risk of gastroesophageal reflux, obesity (BMI >30), anticipated difficult airway, or evidence of cardiac disease. Patients were randomized to two groups (group R=remifentanil, group A=alfentanil) in a double-blind manner by the sealed envelope technique.

All patients received i.v. Hartmann's solution 5 ml kg^{-1} over 5–10 min before the induction of anaesthesia. Routine monitoring was instigated and heart rate and arterial pressure were recorded at 1 min intervals throughout the study. Arterial pressure was measured non-invasively using an automatic oscillometer (Datex Cardiocap II) and ECG was monitored with electrodes in the CM5 position. Three readings of heart rate and arterial pressure were taken before the start of the study and the mean of these three values defined as each individual's baseline data. All patients received i.v. glycopyrrolate 0.2 mg immediately followed by a bolus of either remifentanil (0.5 μg kg^{-1} in 10 ml saline over 30 s) followed by a remifentanil infusion at 0.1 μg kg^{-1} min^{-1} (group R), or a bolus of alfentanil (10 μg kg^{-1} in 20 ml saline over 30 s) followed by an infusion of saline (group A). Immediately after the study drug, anaesthesia was induced with propofol (0.5 mg kg^{-1} followed by 10 mg every 10 s until loss of verbal contact) and rocuronium 0.6 mg kg^{-1} was administered to produce neuromuscular block. Patients' lungs were ventilated manually with 1% isoflurane and 66% nitrous oxide in oxygen, to an end-tidal carbon dioxide tension of 4.0–4.5 kPa. Neuromuscular block was confirmed with a nerve stimulator and laryngoscopy, and tracheal intubation were then performed 3 min after loss of verbal contact.

Table 1 Patient characteristics, view and duration of laryngoscopy: mean (SD, or range), or number There were no significant differences between groups

	Group R (*n*=19)	**Group A** (*n*=20)
Age (yr)	73.1 (65–83)	74.0 (65–85)
Sex (M:F)	9/10	11/9
Weight (kg)	68.8 (15.3)	69.8 (13.5)
ASA grade (I/II/III)	6/11/2	7/12/1
Propofol dose (mg)	76.7 (25.0)	76.1 (23.9)
Grade of anaesthetist intubating (SHO/SpR/Consultant)	3/12/4	2/16/2
Duration of laryngoscopy (s)	14.7 (9.8)	13.4 (8.7)
View at laryngoscopy (1/2/3)	12/6/1	17/2/1

Ephedrine (3 mg increments) was administered for hypotension (systolic arterial pressure (SAP) <100 mm Hg, or a decrease of >30% from baseline values for >60 s) and atropine, in 300 μg increments, for bradycardia (heart rate <45 beats min^{-1}). For hypertension (SAP >200 mm Hg, or an increase of >30% above baseline for >60 s) or tachycardia (heart rate >130 beats min^{-1} for >60 s), the inspired isoflurane concentration was increased in increments of 0.5%. Power calculations based on previous data,[7] suggested that 20 patients per group would detect a 15% difference in SAP or heart rate between the groups after intubation (α=0.05, β=0.2).

Statistical analysis was performed using a general linear model analysis of variance for repeated measures for continuous variables (with treatment group and time as between- and within-group factors, and Bonferroni adjustment for multiple comparisons). All analyses were performed using SPSS for Windows computer software (release 9.0).

One patient in the remifentanil group was excluded because of a procedural violation (unanticipated difficult tracheal intubation with duration of laryngoscopy >2 min). Patient characteristics are given in Table 1. Baseline arterial pressure and heart rate were similar in both groups (Table 2). Mean arterial pressure (MAP) decreased significantly after induction of anaesthesia in both groups ($P<0.05$ compared with baseline values) and increased for 3 min after intubation ($P<0.05$ compared with pre-intubation), but remained below baseline throughout the study period. It was significantly lower than baseline at 4–5 min after intubation in both groups ($P<0.05$). Changes in SAP and diastolic arterial pressure (DAP) followed a similar pattern but DAP was significantly higher in group A at 4 and 5 min post-intubation ($P<0.05$). However, there were no differences between groups in MAP or SAP at any time point.

Table 2 Mean (SD) SAP, DAP, and MAP and heart rate at baseline, after induction of anaesthesia (Ind) and after tracheal intubation (Int) in groups R and A *$P<0.05$ compared with baseline, **$P<0.05$ compared with pre-intubation (Ind+3 min), ***$P<0.05$ between groups. Baseline values are the mean of three readings

	Baseline	**Ind+1 min**	**Ind+2 min**	**Ind+3 min**	**Int+1 min**	**Int+2 min**	**Int+3 min**	**Int+4 min**	**Int+5 min**
Group R									
SAP (mm Hg)	159 (17)	134 (30)*	121 (29)*	104 (23)*	133 (27)**	141 (26)**	129 (30)**	118 (21)*	109 (19)*
DAP (mm Hg)	79 (11)	68 (17)	63 (20)	54 (15)*	77 (18)**	77 (22)**	69 (18)**	60 (15)*, ***	57 (11)*, **
MAP (mm Hg)	103 (11)	82 (21)*	79 (21)*	68 (19)*	96 (18)**	97 (25)**	88 (21)**	78 (20)*	73 (14)*
Heart rate (beats min^{-1})	77 (14)	75 (19)	74 (20)	74 (20)	92 (18)*, **	89 (18)**	82 (19)	79 (18)	77 (17)
Group A									
SAP (mm Hg)	153 (23)	130 (28)*	115 (24)*	105 (19)*	132 (28)**	143 (34)**	135 (32)**	127 (29)*	119 (25)*
DAP (mm Hg)	83 (11)	73 (15)	65 (13)	60 (10)*	84 (16)**	86 (20)**	80 (19)**	74 (17)*, ***	69 (13)*, **
MAP (mm Hg)	106 (15)	90 (18)*	82 (17)*	74 (12)*	101 (23)**	105 (24)**	98 (24)**	89 (20)*	83 (17)*
HR (min^{-1})	77 (10)	78 (10)	77 (12)	77 (12)	97 (15)*, **	94 (15)*, **	91 (17)*, **	88 (16)*, **	86 (15)**

Heart rate increased significantly after intubation in both groups to exceed baseline values. Heart rate remained elevated, compared with pre-intubation values, for 2 min in group R ($P<0.05$) and for 5 min in group A ($P<0.05$). Values after intubation were significantly higher than baseline for 1 min in group R and for 4 min in group A ($P<0.05$). However, there were no between-group differences in heart rate throughout the study.

One patient in group R and two patients in group A experienced marked hypotension (SAP <80 mm Hg for >1 min). Four patients in group R and three in group A required ephedrine for hypotension. However, nine patients in group R and eight in group A had transient hypotension (SAP <100 mm Hg for <1 min) which did not require ephedrine. One patient in group R and two in group A received an increased inspired concentration of isoflurane to treat hypertension. There were no incidences of bradycardia, tachycardia, arrhythmias, ST segment, or other ECG changes observed during the study.

Comment

In this study, the cardiovascular effects of remifentanil and alfentanil at induction of anaesthesia and intubation were similar. Although observed increases in MAP and heart rate at intubation were statistically significant, they were modest and clinically acceptable. MAP remained below baseline values throughout the study, whereas HR exceeded baseline values for 1 (group R) and 4 min (group A) after intubation. DAP was significantly higher in group A than group R at 4 and 5 min after intubation, probably because an infusion of remifentanil was used (group R), whereas the effects of alfentanil would be diminishing by this time (group A).

Mild hypotension (SAP <100 mm Hg for <1 min) after induction of anaesthesia occurred in almost 50% of patients despite i.v. fluid pre-loading and glycopyrrolate pre-treatment, but marked hypotension (SAP <80 mm Hg for >1 min) occurred in only three patients. There was also large variation in response to laryngoscopy and tracheal intubation, with the maximum mean heart rate and arterial pressure occurring 2 min after intubation. Mean SAP, 2 min after tracheal intubation, was 140.6 (range 100–193) and 143.5 (range 92–196) mm Hg in groups R and A, respectively.

These findings suggest that the elderly are susceptible to marked fluctuations in arterial pressure and heart rate at induction of anaesthesia and that attenuation of cardiovascular responses was sometimes incomplete, with large variations between individual patients. However, the overall incidence and degree of hypotension in this study is likely to have been greater, had higher doses of remifentanil or alfentanil been used. Although studies in younger adults have used higher doses of alfentanil, 10 μg kg^{-1} was found to be optimal in elderly patients.[7] The potency of remifentanil compared with alfentanil is approximately 20:1,[8] which corresponds to the remifentanil dose of 0.5 μg kg^{-1} used here. A previous study showed these dose regimens to have similar cardiovascular effects in hypertensive patients.[9]

In another study in elderly patients, the cardiovascular response to tracheal intubation was attenuated by fentanyl 3 μg kg^{-1} but with a 35% incidence of marked hypotension (SAP <80 mm Hg).[10] The incidence of hypotension in the present study may also have stemmed from the use of propofol, despite careful titration of dose to effect. The elderly are known to be sensitive to the effects of propofol,[11] but it has been suggested to be the preferred i.v. anaesthetic agent to attenuate the cardiovascular response to intubation.[12] However, severe hypotension was rare in this study.

Although the drug combinations and doses were reasonable in this group of elderly patients, no patients in this study had significant cardiovascular disease. Few data are available on the effects of remifentanil in patients with impaired cardiac function, although hypotension is more likely to occur, and further studies should investigate the optimum dose of remifentanil in these high-risk patients.

In summary, remifentanil 0.5 μg kg^{-1} over 30 s followed by an infusion of 0.1 μg kg^{-1} min^{-1} was as effective as alfentanil 10 μg kg^{-1} in attenuating the pressor response to tracheal intubation in elderly patients. It is an acceptable alternative to alfentanil at induction of anaesthesia when a remifentanil infusion is used during surgery.

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CASE REPORTS

Management of life-threatening autonomic hyper-reflexia using magnesium sulphate in a patient with a high spinal cord injury in the intensive care unit

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We report the successful use of i.v. magnesium sulphate to control life-threatening autonomic hyper-reflexia associated with chronic spinal cord injury in the intensive care environment. A 37-yr-old, male was admitted to the intensive care unit with a diagnosis of septic shock and acute renal failure secondary to pyelonephritis. He had been found unresponsive at home following a 2-day history of pyrexia and purulent discharge from his suprapubic catheter. He had sustained a T5 spinal cord transection 20 yr previously. Initial management included assisted ventilation, fluid resuscitation, vasopressor support, and continuous veno-venous haemofiltration. The sepsis was treated with antibiotic therapy and percutaneous nephrostomy drainage of the pyonephrosis. On the fifth day, the patient developed profuse diarrhoea. This was associated with paroxysms of systemic hypertension and diaphoresis, his arterial pressure rising on occasion to 240/140 mm Hg. A diagnosis of autonomic hyper-reflexia was made and a bolus dose of magnesium sulphate 5 g was administered over 15 min followed by an infusion of 1–2 g h^{-1}. There was an almost immediate decrease in the severity and frequency of the hypertensive episodes. There were no adverse cardiac effects associated with the administration of magnesium, only a slight decrease in minute ventilation as the plasma level approached the upper end of the therapeutic range (2–4 mmol $litre^{-1}$). In view of the beneficial effects observed in this case we advocate further research into the use of magnesium sulphate in the treatment or prevention of autonomic hyper-reflexia secondary to chronic spinal cord injury in the intensive care unit.

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Autonomic hyper-reflexia is a common and potentially life-threatening complication of chronic spinal cord injury and its control is paramount to the safe care of such patients in the intensive care environment. Intravenous magnesium sulphate has proven useful in controlling paroxysmal hypertension associated with tetanus and phaeochromocytoma.[1] In view of its pharmacological mode of action there is scientific rationale for the use of magnesium in controlling the hypertensive crises of autonomic hyper-reflexia in intensive care.

Case report

A 37-yr-old, 128 kg, Caucasian male was referred to the intensive care unit having been found unresponsive at home following a 2-day history of pyrexia, myalgia, and an offensive discharge from his suprapubic catheter. He had sustained a T5 spinal cord transection in a road traffic accident 20 yr previously that had left him paraplegic. Subsequent recurrent urinary tract infections had led to a hypotrophic, non-functioning right kidney, and multiple

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perinephric abscesses involving the left kidney, for which he had undergone a left partial nephrectomy 4 yr previously. His serum creatinine concentration was normal at 96 µmol litre^{-1}, 6 months before this admission. His history was further complicated by mild asthma and diet-controlled non-insulin-dependent diabetes mellitus. His medication included oral dantrolene 50 mg three times daily and baclofen 10 mg three times daily for muscle spasms, he controlled the headaches associated with autonomic hyper-reflexia with nitroglycerine sublingual spray.

On presentation he had a Glasgow Coma Scale of 4, which improved to 9 with i.v. fluid resuscitation, a tympanic temperature of 38.2°C, a sinus tachycardia of 122 min^{-1} and he was hypotensive (arterial pressure 75/32 mm Hg). He had a neutrophil leucocytosis (24.0×10^9 litre^{-1}), a C-reactive protein concentration of 270 mg litre^{-1}, a blood glucose concentration of 22.6 mmol litre^{-1}, and a base excess of −12. In addition, he was anuric with a serum creatinine concentration of 346 µmol litre^{-1}. An ultrasound scan revealed an absent right kidney, left hydronephrosis, and an empty bladder. A diagnosis of septic shock secondary to pyelonephritis was made and following blood culture the patient was commenced on cefotaxime 1 g three times daily, metronidazole 500 mg twice daily, and gentamicin 4 mg kg^{-1}, the dosing interval being dictated by daily serum gentamicin assays.

Intravenous fluid resuscitation was continued, the airway was secured by orotracheal intubation and artificial ventilation assisted using synchronized intermittent mandatory ventilation with pressure support. Continuous veno-venous haemofiltration was commenced and systolic arterial pressure was maintained above 100 mm Hg with i.v. fluid and norepinephrine 0.015 µg kg^{-1} min^{-1}. Insulin was commenced at 4 units h^{-1} to control blood glucose levels and sedation was maintained with propofol 180 mg h^{-1} and fentanyl 100 µg h^{-1}. Once the patient was stable haemodynamically, a left-sided nephrostomy tube was inserted percutaneously under ultrasound guidance. Blood and urine cultures grew Enterococci and *Proteus* spp.

The patient made good progress and by the fourth day after admission no longer required vasopressor support and was polyuric through the nephrostomy. His white cell count and serum creatinine concentration had fallen to 9.0×10^9 litre^{-1} and 215 µmol litre^{-1}, respectively. Continuous veno-venous haemofiltration was discontinued.

On the fifth day, the patient developed profuse diarrhoea. Shortly afterwards, unpredictable and sudden paroxysms of systemic hypertension started, the arterial blood pressure reaching 240/140 mm Hg on occasion. These episodes were associated with pallor and diaphoresis. The heart rate remained largely unchanged. Rising serum glucose levels were treated by adjusting the continuous i.v. infusion of insulin, which was increased from 4 to 8 units h^{-1}. A diagnosis of autonomic hyper-reflexia was made and sedation was increased such that the patient just coughed on suctioning. Nevertheless, paroxysms of hypertension increased in frequency and severity over the following 24 h. They were thought to be triggered by visceral stimulation associated with the diarrhoeal illness. A bolus dose of magnesium sulphate 5 g (approximately 40 mg kg^{-1}) was administered by slow i.v. injection over a 15-min period with continuous ECG and invasive arterial pressure monitoring. This was followed by an infusion of magnesium sulphate at 1–2 g h^{-1} with the aim of achieving a plasma concentration of 2–4 mmol litre^{-1}.[1] A decrease in both the frequency and severity of the systolic hypertensive episodes was noted almost immediately (Table 1).

The plasma magnesium concentration 12 h before administration of the bolus dose of magnesium sulphate was 0.6 mmol litre^{-1} (normal range 0.7–1.2 mmol litre^{-1}). The plasma magnesium concentration was assayed again at 12, 24, 48, 60, and 84 h after the infusion was commenced and peaked at 5.15 mmol litre^{-1}, 48 h after the infusion was initiated (Table 2). As this was higher than the target plasma concentration (2–4 mmol litre^{-1}), the magnesium infusion was discontinued.

There were no apparent adverse cardiac effects associated with the high plasma magnesium concentration. Initially, there was no significant decrease in minute ventilation, with the patient maintaining normocarbia at 4.9 kPa (normal range 4.8–5.9 kPa) with volume-controlled synchronized intermittent mandatory ventilation with pressure support. (SIMV rate of 12 breaths min^{-1} and pressure support of 14 cm H_2O above 5 cm H_2O PEEP.) However, between 24 and 36 h after the infusion was commenced, the minute ventilation decreased slightly with a corresponding rise in arterial carbon dioxide tension. The respiratory rate, however, remained unaltered (Table 3). This was, therefore, attributed to a decrease in tidal volume. There was no other impairment of gas exchange. At 36 h after commencement of the magnesium infusion, the pressure support was increased to 18 cm H_2O to maintain normocarbia and prevent respiratory acidosis.

Within 12 h of initiation of the magnesium infusion, no further episodes of autonomic hyper-reflexia were noted, in spite of the ongoing diarrhoeal illness. The level of sedation was decreased as the arterial pressure stabilized, although insulin requirements remained high at 8 units h^{-1}. The patient subsequently made an uneventful recovery and was discharged to the ward after 11 days of intensive care.

Discussion

The number of patients with chronic spinal cord injury presenting both to specialist and non-specialist units with medical conditions and for elective surgery is increasing.[2] The management of conditions occurring secondary to spinal cord injury, such as respiratory failure or sepsis from the urinary tract, respiratory tract or skin, can necessitate intervention on intensive care. Of particular concern to the intensivist is autonomic hyper-reflexia, a common and potentially life-threatening condition associated with

Table 1 The maximum, minimum and median systolic pressures over 10 4-h periods before, and 10 4-h periods after administration of magnesium sulphate. The maximum difference in systolic arterial pressures over each 4-h period is also shown. *The first episode of autonomic hyper-reflexia recorded during this 4-h period

	Maximum systolic BP (mm Hg)	Minimum systolic BP (mm Hg)	Median systolic BP (mm Hg)	Maximum difference BP (mm Hg)
Pre-magnesium 4-h periods	155	120	135	35
	140	125	132	15
	175	130	141	45
	155	140	140	15
	200*	110*	122*	90*
	200	110	135	90
	190	115	140	75
	200	150	175	50
	240	130	210	110
	220	150	190	70
Post-magnesium 4-h periods	160	110	130	50
	177	100	115	77
	150	115	120	35
	130	100	117	30
	155	115	130	40
	160	150	155	10
	160	135	147	25
	130	120	127	10
	125	115	120	10
	115	100	100	5

Table 2 The plasma magnesium concentration and the infusion rates of magnesium sulphate from 12 h prior to magnesium being commenced, to 84 h after initiation of therapy. The corresponding serum creatinine levels are also shown

Magnesium bolus	Mg concentration (mmol litre^{-1})	Mg infusion rate (g h^{-1})	Creatinine (μmol l^{-1})
12 h before	0.6	0	151
12 h after	3.72	2	162
24 h after	3.95	2	176
48 h after	5.15	1	197
60 h after	3.02	0	164
84 h after	1.95	0	150

Table 3 The mean (SD) minute ventilation, arterial carbon dioxide tension (Pa_{CO_2}), and respiratory rate (RR) in the 12 h period before, and in the first three 12 h periods subsequent to the magnesium infusion being commenced

	12–0 h pre Mg	0–12 h post Mg	12–24 h post Mg	24–36 h post Mg
Minute ventilation (litre)	16.54 (2.45)	15.75 (2.99)	16.34 (3.04)	12.88 (2.54)
Pa_{CO_2} (kPa)	4.66 (0.12)	4.66 (0.25)	4.90 (0.30)	6.34 (1.19)
RR (breaths min^{-1})	17.75 (2.22)	16.33 (3.84)	17.41 (3.36)	16.25 (3.54)

chronic spinal cord lesions. It is characterized by an uninhibited sympathetic response producing headache, flushing, and diaphoresis above the level of the lesion, together with pallor and piloerection in the lower trunk. Reflex bradycardia often accompanies the hypertension, which may be severe and prolonged. Some or all of these features may be present. Autonomic hyper-reflexia can complicate both complete and partial lesions of the spinal cord and its prevalence varies with the height of the lesion, being more common in higher spinal cord injury. It has been described in lesions above T10,[3] and has a prevalence of 60–80% in lesions above T6.[4,5] The onset of autonomic hyper-reflexia most commonly occurs in the reflexic stage of the condition, usually between 3 weeks and 12 yr after injury, but recent case reports indicate an earlier onset (within 7 days) in some patients during the flaccid phase.[6,7] The complications of autonomic hyper-reflexia, which include myocardial ischaemia, cerebral haemorrhage, coma, and death, are attributable to the hypertensive crises, which follow uncontrolled paroxysms of sympathetic activity. It is of interest that our patient had a history of headaches associated with autonomic hyper-reflexia for which he used nitroglycerine sublingual spray. Such a history in a patient with chronic spinal cord injury should alert the intensivist to the likelihood of the patient developing autonomic hyper-reflexia when acutely ill.

Autonomic hyper-reflexia can be stimulated either by visceral or, less commonly, cutaneous stimuli below the level of the lesion. Patients with high spinal cord injury on intensive care units may be exposed to such stimuli. These include catheterization and distension of the urinary bladder, urinary tract infections, enemata, sigmoidoscopy, various causes of gastrointestinal distension, and manipulation of pressure sores.[7]

The pathophysiology of autonomic hyper-reflexia involves the loss of higher centre inhibition of sympathetic outflow. More importantly, however, it results from disorganized connections between pre-synaptic afferent terminal buttons (which multiply chaotically after cord injury) and interneurones within the spinal cord, which in turn synapse with sympathetic efferents.[2] Patients with chronic injury to the spinal cord are also known to have decreased levels of circulating catecholamines and an increased sensitivity to norepinephrine.[7] In addition, plasma norepinephrine levels rise markedly during episodes of autonomic hyper-reflexia.[7]

The management of autonomic hyper-reflexia requires removal of the precipitating stimulus when possible, and if necessary pharmacological intervention. In the intensive care unit it may not be possible easily to avoid, remove, or treat the precipitating stimulus, and pharmacological intervention then becomes necessary to prevent and treat life-threatening complications. Drug therapies include alpha-1 adrenoceptor blockers, beta-adrenoceptor blockers, calcium channel antagonists, alpha-2 adrenoceptor agonists, ganglion blockers, nitrates, hydralazine, and reserpine.[2,6,7,8] Many of these drugs and also magnesium sulphate have played a part in the management of the paroxysms of systemic hypertension associated with tetanus and phaeochromocytoma.[1,9,10]

Magnesium controls catecholamine-induced hypertensive crises through several anti-adrenergic mechanisms of which calcium antagonism is of primary importance.[11] Magnesium is an essential regulator of calcium movement in and out of the cell, and of the actions of calcium within the cell.[12] In addition, magnesium competes with calcium for transmembrane channels. By these mechanisms, magnesium inhibits catecholamine release both from the adrenal medulla and from adrenergic nerve endings. Magnesium causes a reduction of systemic vascular resistance by a direct vasodilator effect on vessel walls and by direct blockade of catecholamine receptors.[12] Magnesium possesses anti-arrhythmic properties, and offers protection from catecholamine-induced myocarditis by the preservation of intracellular adenosine triphosphate and glycogen stores and by reducing lactate production.[1,9,11–13] The serum concentration required to exert these effects is in the range of 2–4 mmol litre^{-1}.[1]

Although magnesium has a high therapeutic index, at plasma levels above 2.5 mmol litre^{-1}, it causes muscle weakness by the dose-dependent inhibition of acetylcholine release in peripheral nerves. Loss of tendon reflexes occurs at a plasma concentration above 5 mmol litre^{-1} and respiratory depression above 7 mmol litre^{-1}.[11] Muscle weakness from magnesium administration is thought to develop more rapidly if commenced in the presence of sedation.[14] Small but significant reductions in pulmonary function have been reported in pre-eclamptic patients in labour receiving magnesium sulphate infusions, with plasma concentrations in the therapeutic range.[15] Respiratory insufficiency is a common consequence of spinal cord injury and results mainly from muscle weakness, although there is some data to suggest that reductions in respiratory drive and ventilatory response to hypercapnia also occur.[2] We therefore emphasize the ready availability of ventilatory support when administering large doses of magnesium sulphate to patients with high spinal cord injury.

Our patient was receiving ventilatory support and sedation throughout the administration of magnesium, and a decrease in minute ventilation only became apparent as the plasma level of magnesium approached the upper limit of the targeted range. The rapid rate of change of magnesium concentration was, however, probably due to the patient's renal dysfunction. Frequent monitoring of plasma levels of magnesium is essential especially in the presence of renal dysfunction, and in view of the fact that clinical assessment of muscle weakness may prove impossible in sedated patients and in patients with chronic spinal cord injury.

In a recent case report, Maehama, Izena and Kanazawa describe the successful use of magnesium sulphate in the management of autonomic hyper-reflexia occurring during labour in a patient with high spinal cord injury.[16] Our case report highlights this serious complication of spinal cord injury in the intensive care setting and introduces the use of magnesium sulphate for its management. In view of its pharmacological mode of action, its wide therapeutic index in the ventilated patient, and its successful use in the management of other systemic hypertensive crises mediated by the autonomic nervous system, we advocate further research into the use of magnesium sulphate in the treatment or prevention of autonomic hyper-reflexia secondary to chronic spinal cord injury in the intensive care unit.

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Lumbar ependymoma presenting with paraplegia following attempted spinal anaesthesia

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Neurological deterioration from intraspinal haematoma following insertion of a spinal needle is extremely rare. We present the case of a 28-yr-old female, who presented with complete paraplegia following attempted spinal anaesthesia for delivery of her third child. Space-occupying iatrogenic spinal haemorrhage from a previously undiagnosed lumbar ependymoma was found to be the precipitating cause. Following laminotomy with blood clot and tumour removal her neurological function improved.

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Intraspinal haemorrhage as a cause of neurological complications following insertion of a spinal needle for lumbar puncture, epidural, or spinal anaesthesia is extremely rare. In several large series reviewed by Sage,[1] including over 100 000 procedures, no such occurrence was observed. However, multiple reports concerning intraspinal haematomas with neurological deterioration following spinal needle insertion exist. A bleeding diathesis could be identified in approximately 70% of these cases.[1]

We present the case of a young female who suffered from complete paraplegia caused by intraspinal haemorrhage from a previously undiagnosed lumbar ependymoma after attempted spinal anaesthesia for Caesarean section.

Case report

A 28-yr-old gravida 3, para 2, underwent Caesarean section for the delivery of her third child. After an unsuccessful attempt at spinal anaesthesia with a 27G needle at the L1-2 level, where neither cerebrospinal fluid nor blood was obtained, general anaesthesia was performed because of the urgency of the case. The operation was without complications and immediately afterwards the patient tolerated the procedure well.

Approximately 12 h later, the patient started to complain of mild paraesthesia in both feet and calves. During the night she experienced increasing low back pain radiating

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into both legs. The next morning she presented with complete paraplegia and anaesthesia from L1, including urinary retention and absent anal sphincter tone. Following emergency referral to our institution a MRI showed extended intraspinal bleeding from Th12 to L2. Approximately 8 h after the patient was found to be paraplegic, a laminotomy from Th12 to L2 was performed. As well as the intradural blood clot, blue-greyish tumour tissue in the conal region was identified and removed with preservation of all neural structures. Neuropathological examination revealed an ependymoma with massive intratumoural haemorrhage.

Postoperatively, no bleeding disorder was found. The patient could not remember any signs suggestive of the neoplasm during her pregnancy. Eight months later, her motor function is slowly improving, allowing her to stand up from the wheelchair without assistance and to walk about 5 m with crutches. She has regained bowel function but bladder function is still absent.

Discussion

In 1946 Nicholson and colleagues[2] mentioned the possible neurological complications of spinal anaesthesia in the presence of previously undiagnosed spinal space-occupying tumours. The authors considered the neurological complications mainly attributable to the occurrence of neurotoxic effects caused by the injected anaesthetic agent which could not be diluted appropriately, due to impaired flow of cerebrospinal fluid caused by the lesion. Furthermore, the risk of neurological deterioration following lumbar puncture below a spinal subarachnoid block has been shown to be at least as high as 14%.[3] In these cases, the mechanism of 'spinal coning' through exacerbation of pressure differentials above and below the block following removal of cerebrospinal fluid has been suggested.

The first report of neurological complications in connection with iatrogenic haemorrhage from a spinal neoplasm was by Roscoe and colleagues in 1984.[4] They reported a 24-yr-old parturient, who, 3 days after uneventful epidural analgesia at the L2-3 interspace, developed increasing low back pain and bladder dysfunction, together with gradual worsening of motor and sensory function in both legs. In the emergent decompressive laminectomy 17 h after the onset of neurological symptoms, dural perforation of the distended thecal sac was found and an ependymoma with intratumoural haemorrhage was excised. The patient made an almost complete recovery with intact bladder function and ability to walk with leg brace support.

Since then, two additional cases of similar pathology have been described. Bredtmann and colleagues[5] reported haemorrhage from a tumour in a 58-yr-old male following uneventful subarachnoid injection of the anaesthetic agent after clear CSF was obtained at the L3-4 level. Starting 6 h later, the patient developed severe low back pain, headaches, and meningism. Laminectomy was performed 3 days after onset of symptoms and an ependymoma at L3-4, together with an intradural blod clot, was removed. The patient recovered completely.

In a 79-yr-old female, several attempts of epidural anaesthesia were performed in vain at the L2-3 and L3-4 interspaces.[6] The epidural space could not be located precisely. It was then decided to perform general anaesthesia. Over the next 3 weeks the patient experienced the development of almost complete paraplegia. In the subsequent laminectomy, an ependymoma with massive intratumoural haemorrhage was removed and the patient made a satisfactory recovery of motor and autonomic function. In the last two reports described, both patients retrospectively complained of a history of increasing radicular pain in both legs preoperatively, but these symptoms were not appropriately diagnosed by the responsible physicians.

Reviewing these reports of neurological malfunction following puncture into an undiagnosed lumbar tumour and subsequent haemorrhage, we found that in all four cases (including the one presented in this paper) the haemorrhage arose from an ependymoma. These intradural neoplasms of the cauda equina and conal region are thought to be prone to haemorrhage due to their vascular structure[7] and are known to present with spontaneous bleeding.[8] Despite the intradural location of ependymomas, the hazards of iatrogenic haemorrhage do not solely occur after spinal anaesthesia, they occur also after epidural anaesthesia. The thecal sac, distended by the tumour, together with a compressed epidural space, is likely to be punctured with subsequent injury of the underlying fragile tumour vessels. In contrast, however, ependymomas do not necessarily bleed after massive manipulation with a spinal needle.[9]

We found that, in two of the four cases, regional blockade was performed in labour for either analgesia or Caesarean section. In the series of ependymomas of the cauda region described by Schweitzer and colleagues,[9] the coincidence of pregnancy and this tumour type has already been described, as two of their six female patients first experienced symptoms during pregnancy. The most common age for ependymomas of the conus and cauda region is the third decade so this association is not surprising. The mean duration of symptoms before diagnosis is 28–35 months,[9 10] suggesting slow tumour growth. During pregnancy, increased intradural pressure may aggravate the onset of symptoms.

This report draws attention to the need for careful evaluation of symptoms suggesting the presence of a spinal mass, before lumbar puncture, peridural, or spinal anaesthesia is planned. In patients complaining of a history of increasing low back pain, bladder dysfunction, weakness, or paraesthesias of the lower limbs, we strongly recommend postponing the procedure. In an emergency situation, however, spinal anaesthesia should not be attempted and general anaesthesia should be undertaken.

Postprocedural observation always needs to rule out signs of increasing lumbar root compression, even in otherwise healthy young women after delivery. Interestingly, in all cases described, the onset of neurological deterioration was not immediately after the lumbar puncture. First symptoms occurred 6 h after the operation at the earliest and 3 days at the latest. If spinal bleeding is suspected, a MRI of the lumbar and lower thoracic spine is considered the appropriate diagnostic tool.

Prompt surgical evacuation of a symptomatic lumbar haematoma resulting from tumoural bleeding should always be attempted. Even in the presence of severe neurological dysfunction for hours and even weeks, all patients made at least a partial recovery, resulting in significantly diminished morbidity.[8]

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Intraoperative pulmonary oedema in a child following systemic absorption of phenylephrine eyedrops

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Ophthalmic surgeons often apply phenylephrine topically to effect pupillary dilatation. We describe a paediatric patient in whom cardiac arrhythmias, severe hypertension and pulmonary oedema occurred following intraoperative ocular phenylephrine administration. We believe that systemic absorption of the drug was responsible and discuss ways in which this might be reduced when ocular phenylephrine is used in this context.

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Topical phenylephrine solutions are widely used in ophthalmic surgery, both for capillary decongestion and for pupillary dilatation. Phenylephrine is predominately an α-adrenoreceptor agonist and significant systemic absorption can occur after topical administration. Adverse consequences in adults have included hypertensive crisis,[1 2] tachycardia, reflex bradycardia and ventricular arrhythmias,[2] and myocardial infarction and cardiac arrest.[3] However, despite theoretical concerns about neonatal subarachnoid haemorrhage,[4] serious morbidity associated

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with hypertension is uncommon in paediatric patients following systemic absorption of ocular phenylephrine. We describe intraoperative complications occurring in a paediatric patient that appear to have been caused in this way. Strategies for reducing systemic phenylephrine absorption and potentially reducing the risks of similar episodes are discussed.

Case report

An 8-year-old boy weighing 37.7 kg was admitted for right retinal detachment surgery. He had undergone previous uneventful ophthalmological surgery and had no significant past medical or family history. Topical local anaesthetic cream was applied to the dorsum of both hands on the ward but he failed to receive the preoperative ocular medication he had been prescribed, namely four drops of phenylephrine 2.5% and cyclopentolate 1% to each eye.

In the anaesthetic room, anaesthesia was induced with sevoflurane in oxygen. Following insertion of a 22-gauge cannula, the patient received propofol 40 mg, vecuronium 4 mg, alfentanil 250 µg and morphine 1.5 mg i.v. He was also given ondansetron 3.5 mg i.v., and diclofenac and paracetamol suppositories (37.5 mg and 500 mg, respectively). A size-3 laryngeal mask was inserted and manual ventilation commenced with 60% nitrous oxide and 1% isoflurane in oxygen. He was then transferred to the operating theatre and routine monitoring was applied. Mechanical ventilation was commenced via a circle circuit with carbon dioxide absorption and adjusted to maintain peak airway pressure below 20 cm H_2O. At all times intraoperatively, end-tidal carbon dioxide concentration was 5.3 kPa or less.

On the operating table, before incision, the operating surgeon noticed that the pupil was not dilated and between two and five drops of 10% aqueous phenylephrine (40–50 µl per drop) were administered topically to the right eye by the assistant surgeon, without the anaesthetist's knowledge. Five minutes into surgery, traction on the extra-ocular muscles precipitated a sinus bradycardia of 40 beats min^{-1}. Glycopyrrolate 0.2 mg was administered intravenously and the heart rate increased to 80 beats min^{-1}.

Several minutes later, non-invasive systolic arterial pressure rose from 95 to 211 mm Hg and the heart rate from 80 to 160 beats min^{-1}. The electrocardiogram showed frequent multifocal atrial and ventricular ectopic beats. The inspired isoflurane concentration was increased and the earlier administration of ocular phenylephrine was confirmed by the assistant surgeon on questioning. A diagnosis of hypertension and arrhythmias secondary to systemic absorption of ocular phenylephrine was made. Intravenous labetalol was given in 5 mg increments to a total of 25 mg over the next 10 min until the heart rate and blood pressure returned to normal.

A few minutes later, the monitors displayed a reduced tidal volume with unchanged airway pressures. With an inspired oxygen concentration (FI_{O_2}) of 30%, oxygen saturation decreased to 88%. Auscultation of the chest revealed scant basal crepitations. Oxygen saturation returned to normal after a few minutes on increasing FI_{O_2} to 60% and ventilating manually. Mechanical ventilation was recommenced and FI_{O_2} gradually reduced back to 30% over 30 min with no further desaturation.

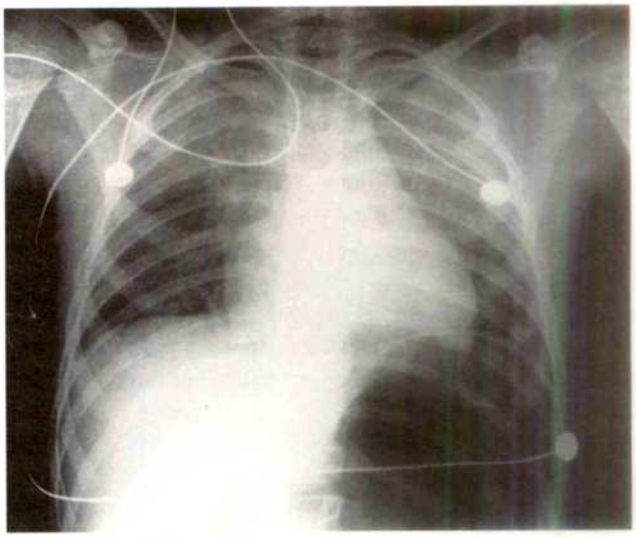

Fig 1 Anteroposterior chest radiograph revealing pulmonary oedema and a large gastric air bubble.

Auscultation was repeated after surgical closure. Crepitations were heard throughout the chest and 100 ml bloodstained fluid was aspirated from the trachea using a suction catheter passed via the laryngeal mask. Neuromuscular blockade was reversed and, on resuming spontaneous ventilation, the patient maintained satisfactory tidal volumes, respiratory rate and oxygen saturation. When the patient regained consciousness, the laryngeal mask was removed and he was transferred to the recovery room. Postoperative chest radiography revealed pulmonary oedema (Fig. 1). A postoperative 12-lead electrocardiogram was normal and cardiac enzymes were not raised. Oxygen 4 litre min^{-1} was administered through a face mask for 8 h postoperatively. The patient was discharged the next day with almost complete resolution of radiographic signs.

Discussion

The case described appears to be one of pulmonary oedema in a paediatric patient following an iatrogenic hypertensive crisis with cardiac arrhythmias. The drug most likely to have been responsible was ocular phenylephrine.

Other factors may have had a causative or contributory role in these complications, which have not been described before in similar circumstances. Although the intraoperative end-tidal carbon dioxide concentration was 5.3 kPa or less, it is possible that arterial carbon dioxide concentration was supranormal. This may have predisposed the patient to cardiac arrythmias in the presence of a sympathomimetic agent.

An alternative explanation for the acute pulmonary oedema we observed might have been regurgitation and aspiration of stomach contents. The large gastric air bubble evident in Figure 1 suggests gastric insufflation as a result of ventilation via the laryngeal mask. If this occurred in the initial stages of anaesthesia, despite low airway pressures, it might have predisposed to later regurgitation. The laryngeal mask would not have protected the patient from subsequent pulmonary aspiration. However, this hypothesis disregards the haemodynamic events and the temporal relationship between them and the development of respiratory signs. We believe that gastric insufflation occurred after the development of pulmonary oedema, as a result of high airway pressures attained during manual ventilation of poorly compliant lungs via the laryngeal mask.

Although some regard the technique as controversial, intermittent positive-pressure ventilation via the laryngeal mask in children is widely practised.[5] The risk of clinically significant gastric insufflation is said to be small provided cautious ventilation, with modest tidal volumes and low airway pressures, is employed. Airway integrity, gas leak and abdominal distension should be closely monitored.[6] In our case, gastric insufflation would probably not have arisen had a tracheal tube been used. A tracheal tube would also have allowed us to ventilate at higher airway pressures during resuscitation, thereby potentially reducing the degree of pulmonary oedema (albeit at the risk of barotrauma).

It might be argued that a pure α-adrenergic antagonist should have been used to treat the hypertensive effect of absorbed phenylephrine. Labetalol's β-antagonist activity is between five and ten times greater than its α activity[7] and may have contributed to failure of the left ventricle. However, phenylephrine is known to have β-agonist actions at high doses.[7] The tachycardia and multifocal ventricular ectopics seen in our patient were suggestive of such an effect and represented the most immediate threat to life. In these particular circumstances, with no other indication of the relative predominance of phenylephrine's α and β effects, and in the knowledge that intravenous α-adrenergic antagonists like phentolamine may cause tachycardia,[7] labetolol's predominant β antagonism seemed to be therapeutically appropriate.

Phenylephrine solutions for ocular administration are available in 2.5% and 10% solutions. The 1% solution available for intravenous administration is usually diluted even further by anaesthetists, so doses used in the eye are high by systemic standards. Several techniques have been advocated for achieving effective mydriasis with ocular phenylephrine while reducing systemic absorption and associated haemodynamic effects. These include the use of 2.5% rather than 10% solutions,[8] 8–10 μl rather than 30–32 μl drops,[9–11] eyelid closure,[11] punctuate occlusion and blotting away excess drops after administration of the drug.[4]

From the case described above, we would also recommend that intraoperative administration of ocular drugs by the surgeon should be conducted only after consulting the anaesthetist. The risk of substantial systemic absorption may be increased if ocular incision is performed very soon after administration of such drugs, as in this case.

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Value of bispectral index monitoring during cardiopulmonary resuscitation

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A 67-yr-old man, undergoing pulmonary metastasis resection, experienced a postoperative cardiopulmonary arrest as a result of severe bleeding. Cardiopulmonary resuscitation (CPR) was initiated, then bispectral index (BIS) monitoring was used which reassured the medical team of the adequacy of the resuscitation.

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Keywords: heart, cardiopulmonary resuscitation; monitoring, bispectral index

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Success of cardiopulmonary resuscitation (CPR) in a patient following cardiopulmonary arrest depends mainly on early initiation of advanced cardiac life support and on knowledge of the underlying cause of the arrest. Tenacity of the medical team is also crucial. Although the standard of care for CPR is defined by guidelines,[1] the efficacy of resuscitation would be improved if a device for evaluation of cerebral oxygenation was available.

We present a case in which the use of a device monitoring the bispectral index (BIS) reassured the medical team of the adequacy of CPR.

Case report

The patient was a 67-yr-old man classified as ASA III and undergoing pulmonary metastasis resection. Surgery was performed via a left thoracotomy under general anaesthesia combined with thoracic epidural anaesthesia. A left upper lobectomy was performed with concomitant resection of metastases located in the left lower lobe. During the procedure, the pulmonary artery was lacerated leading to an estimated blood loss of 2000 ml. The patient received 4 units of packed red blood cells (packed RBCs) intraoperatively and was extubated at the end of surgery.

The immediate postoperative period was uneventful and postoperatively, epidural analgesia was initiated. During the first 6 h post-operation, 800 ml of blood drained through the chest tubes. During this period the patient received 2 units of packed RBCs, and after transfusion the haemoglobin level was 8.9 g dl^{-1}. Suddenly, the nurses were alerted to a bradycardia (heart rate of 45 beats min^{-1}): the patient was tachypnoeic, his arterial pressure was unmeasurable, and he became comatose within a few seconds. Intubation, ventilation, and external chest compression were initiated. Physical examination revealed no jugular venous distension but dullness to percussion over the left side of the chest. Extensive bleeding was noted through and around the chest tubes. Major intravascular volume loading was initiated (first with colloid solutions then with packed RBCs) together with the i.v. administration of several boluses of epinephrine 1 mg followed by a continuous epinephrine infusion of 8 mg h^{-1}. Fluctuations in end-tidal carbon dioxide between 10 and 15 mm Hg demonstrated the relative efficacy of resuscitation. Immediately after tracheal intubation, arterial blood gases revealed a metabolic acidosis (pH=7.14, Pa_{CO_2}=44.3 mm Hg, Pa_{O_2}=454 mm Hg, base excess=−13.3, alkali reserve=14.5 mmol $litre^{-1}$ and lactate concentration=7.1 mmol $litre^{-1}$ serum). Potassium was 6.3 mmol $litre^{-1}$ and the haemoglobin level was 8.6 g dl^{-1}. While CPR continued, the patient, whose pupils were unreactive and fully dilated, was transferred to the operating room. Surgery began without anaesthesia. CPR was continued as effectively as possible given the technical difficulties, first by manual external chest compression and then by internal cardiac compression. The surgeon clamped the left pulmonary artery with his fingers. At this time, a member of the team considered placement of Bispectral Index monitoring (Aspect, A-2000™ BIS® Monitor) which displayed an initial value of 80. Pupillary light reflexes were still absent bilaterally. As a BIS of 80 corresponds to a 'normal' level of awakening, the patient received etomidate 10 mg and sufentanil 75 µg intravenously resulting in a decrease of the BIS to 40.

Bleeding stopped, and with CPR haemodynamic stabilization was achieved 15 min later. At the end of surgery, both pupils were still fully dilated and not reacting to light. The

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continuous infusion of epinephrine was progressively reduced to 1.5 mg h^{-1}. One hour later, clinical signs of improvement (limb mobility) were apparent along with an increase in BIS to 90. The patient was transferred to the intensive care unit, weaned from mechanical ventilation at day 4, discharged from the ICU on day 10, and discharged home on the 48th postoperative day. Neurological examination was normal but no psychomotor tests have been performed.

Discussion

This case report shows the potential benefit of BIS monitoring during resuscitation from cardiopulmonary arrest.

The efficacy of CPR is usually based on recovery of consciousness and on the return of neurological signs indicating normal cerebral function. In the absence of such signs, restoration of adequate arterial pressure and a normal end-tidal carbon dioxide level[2] indicate that CPR manoeuvres are effective. The clinical finding of bilateral pupillary dilation with loss of pupillary light reflexes is a late sign of ischaemic brain injury but was of little prognostic value in this case as it may be due to epinephrine administration. The availability of a device providing direct signs of cerebral oxygenation would be useful.

It is uncommon for cardiac arrest to occur in a patient being monitored by an electroencephalogram (EEG). Such a case was reported by Losasso and colleagues,[3] in a patient undergoing carotid endarterectomy who developed asystole during surgical manipulation of the carotid artery. The EEG showed generalized suppression approximately 20 s after the onset of asystole, and low-voltage high-frequency activity after initiation of manual chest compression. Successful resuscitation was associated with the return of an EEG similar to the recording obtained just before the asystole, which had lasted 2 min. The same 10- to 15-s delay between cardiac arrest and the onset of EEG changes had been reported previously.[4] The use of compressed spectral array EEG monitoring during cardiac arrest and resuscitation has also been reported by Young and colleagues.[5]

Recently, changes in the BIS during a hypovolaemic cardiac arrest occurring 4 min after the start of sternotomy were reported.[6] Acute changes in the EEG spectrum lagged behind the decrease in arterial pressure, probably because of the smoothing algorithm used to calculate the BIS cerebral autoregulation causing a lag between the decrease in arterial pressure, the decrease in cerebral blood flow and brain dysfunction may have also been responsible. In the report by England,[6] the BIS returned to the pre-cardiac arrest value once adequate cerebral blood flow had been restored.

The BIS used during this incident is widely available in the operating theatre and provides useful information on the patient's hypnotic state.[7] While there is no proven correlation between the postoperative condition of the patient condition and to BIS values recorded during an emergency, our case report emphasizes the potential value of BIS monitoring during cardiac arrest.

A high BIS value reflects cerebral activity and should encourage the team to continue CPR; a low BIS is much more difficult to interpret and cannot be used as a reason to stop it.

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BJA

HISTORY

The British Journal of Anaesthesia

An informal history of the first 25 years

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In 1961, some 7 months after starting anaesthesia in the Leeds General Infirmary, I took out a subscription to the *British Journal of Anaesthesia*. It cost £3.15s.0d (£3.75) a year. The publishers (John Sherratt and Son of Altringham) sent me the back numbers from the start of that year. I first had a paper published in the journal in 1965; first refereed a paper in 1969; joined the editorial board in 1975; and lasted there until 1998.

The following account of the early years of the journal derives from the journal itself, and from records, letters and minutes of meetings kindly given to me by Dr Edmund Riding and Professor Andrew Hunter when they demitted offices with the journal. The history cannot be complete. Sadly, the earliest minutes books are lost. But there is much of interest covering the times when anaesthesia developed from the rag-and-bottle inhalation era to the use of intravenous anaesthetics, neuromuscular blocking agents, ventilators and monitoring. Thoracic and neurosurgical anaesthesia were revolutionized; cardiac surgery became possible; and resuscitation with intravenous fluids, blood and plasma all developed. Antibiotics improved care. Anaesthetists pioneered intensive care and latterly extended their roles in pain relief outside the operating theatre. All these developments have appeared in papers at some time in this journal. This is a personal view of the journal over its first 25 years: there will be errors and misinterpretations – these are mine.

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The first years: 1923–1929

In 1923, the journal started as the second English language journal devoted entirely to anaesthesia. *Current Researches in Anesthesia* edited by F.H. McMechan beat it by a year. That journal was published in the United States and is now *Anesthesia and Analgesia*. This journal's editor was also an American – Dr Hyman M. Cohen – but one who worked in Manchester. Others on the initial board were: Drs F. Shipway, J. Blomfield, H. E. G. Boyle, D. W. Buxton, all from London, H. B. Fairlie from Glasgow, S. R. Wilson from Manchester, and A. J. O'Leary from Liverpool. The journal was to appear quarterly and cost £2.0s.0d (£2.00) for the four issues. The volumes started in July – which makes citing references somewhat of a problem.

Dr Hyman Maurice Cohen (Figure 1) was born in New York on Christmas day in 1875. He chose a military career and was educated at military academies. After Harvard he went to Baltimore, where he gained his MD. He served with the United States Army, including a period of active duty in the Philippines in 1898. In 1904 he married a Manchester girl. In 1913, having resigned his commission, he came to the United Kingdom. Enrolling at St Bartholomew's Hospital in London, he qualified MRCS, LRCP in 1916. Settling in Manchester, he became a full-time anaesthetist. He maintained contact with his American colleagues. One of his associates in Manchester, Dr S. R. Wilson, held the post of lecturer in physiology at the university there. Together with H. E. G. Boyle, they were the principal founders of the journal.

Dr Cohen's foreword to the first issue[1] is fascinating. He introduces the journal as a publication 'devoted entirely to the interests of Anaesthesia and its practitioners'. It is 'hoped to be able to keep abreast of the

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Fig 1 Dr H. M. Cohen. Editor from 1923 to 1928. Reproduced with permission from the *British Journal of Anaesthesia* 1929; **7**: 48.

times in all that appertains to Anaesthesia and reflect the progress our Speciality is making everywhere'. It was not only to be a 'mouthpiece for those who desire to give public expression to the results of their research' but to 'place before its readers an account of what is being done generally in the anaesthetic world'. The foreword ends with a plea for an organization for the general body of anaesthetists. He noted that 'with the exception of the Section [of Anaesthetics of the Royal Society of Medicine; RSM] in London and the Society [of Scottish Anaesthetists] in Scotland, the general majority of the something like 500 Practitioners of Anaesthesia have no affiliations with similar bodies'. Cohen concludes, 'It is a self-evident fact that anaesthetists united in one large, virile body can do much to advance the science and practice of anaesthesia, and it behoves those of us who are alive to the possibilities of unity to give the matter attention and thought'. It was 10 years before the Association of Anaesthetists of Great Britain and Ireland (AAGBI) was formed, and 25 years before the Faculty of Anaesthetists was founded – two bodies, not one. As Dr Riding (personal communication) has commented, 'this was a very far-sighted editorial'.

What was in the early journals?

I have counted 115 editorials and main articles in the time when Cohen was the editor. There were reviews and reprinted articles from other journals and reports of meetings. The correspondence section started, and there were even the odd humorous items. To wit, in 1925:

Visitor 'Is your daddy in?'

Small daughter 'No, he is out giving an anaesthetic.'

Visitor 'An anaesthetic. That is a big word. What does it mean?'

Small daughter 'Five guineas.'

That would have been a large fee then. In 1928, the editorial described the abysmal payments made to hospital anaesthetists.[2] Other editorials discussed topics such as postoperative lung complications,[3] and research.[4]

History played a large part, as did reports or notices of overseas meetings. Cohen kept up with his American colleagues. In 1926, a party from North America, including McKesson, Wesley Bourne and McMechan, visited the United Kingdom. Dr Cohen was the principal host. There was a joint meeting with the Anaesthetic Section of the RSM.[5] The next year, Cohen visited the United States and at the meeting of the International Anaesthesia Research Society he gave a paper on the value of anaesthetic journals.[6] At a formal session he was presented with a scroll 'For Meritorious Services to the Specialty of Anesthesia', which lists all the then current members of the editorial board of the journal. The scroll was reproduced in the journal in 1927.[7] The other two people honoured at the same session were Arno B. Luckhardt, who had pioneered the use of ethylene as an anaesthetic, and Dr Carl Koller, who, in 1884, had studied the effects of cocaine and introduced it as a local anaesthetic for ophthalmic surgery. Good company.

The early intention was to produce an international journal. Of the original papers in Cohen's time, 48 came from the United Kingdom, 34 from the United States of America, eight from Canada, four from Germany, two each from France, Austria and Italy, and one from Sweden. The North American authors included such pioneers as McKesson, Gwathmey, Leake, Labat, Pitkin, Bourne and McMechan. McMechan, a corresponding member of the editorial board, edited *Current Researches in Anesthesia and Analgesia*. The link between the two journals has been maintained. The journals worked together to initiate the production of the CD version (TEAL) together with *Anesthesiology* and the *Canadian Journal of Anaesthesia* in 1996.

Other early papers covered a variety of topics: obstetric analgesia, epidural block, lung problems, anaesthetic techniques, teaching of anaesthesia to medical students, the reflex basis of anaesthesia, anaesthetic history, and cardiac resuscitation all appear in the first volume. Later, there were articles on: acid–base balance, the use of acetylene and ethylene, the problems for diabetics, the risks of anaesthesia

Fig 2 Dr Joseph Blomfield. The journal's second editor, from 1929 to 1948. Reproduced with permission from *Anaesthesia* 1949; **4**: 90.

and surgery, the dangers of static electricity, body temperature during anaesthesia, the value of regional anaesthesia, 'Avertin' (tribromoethanol, bromethol) anaesthesia, the metabolic consequences of anaesthesia (blood sugar estimations), and premedication. Many repay reading and assessment in the light of modern practice.

In 1927, the editorial board lost its secretary and treasurer. Sidney Rawson Wilson was a Manchester graduate and an anaesthetist at the Royal Infirmary. He was the first appointed Lecturer in Anaesthetics at Manchester University. His physiological and pharmacological interests were well respected. At the time of his death, he was conducting experiments on himself on the effects of various mixtures of nitrous oxide and oxygen. It appears that with his last experiment at home, the oxygen cylinder ran out and he died from anoxia. He was born in 1882 and was obviously an outstanding student in his time at Manchester. As a student, he spent time coaching his fellow students. His interests at the time of his death also included the use of ethylene, and studies of unexpected deaths during ether anaesthesia. He thought these were due to 'impure' ether.

Dr Cohen suffered from hypertension and seems to have had at least one myocardial infarct. He died suddenly whilst motoring in Derbyshire on 31st August 1929. His obituary was written by Sir d'Arcy Power and appears in the next issue of the journal.[8] That issue was delayed by 3 months whilst the new editor took over.

The years under Joseph Blomfield: 1930–1948

Joseph Blomfield (Figure 2) was one of the founders of the journal. When Cohen died, he became editor and stayed in post for the next 18 years. He was born in 1870, the son of Luis Blumfeld. His surname changed during the First World War. Marrying twice, his surviving wife, Kathleen, was the secretary of the Society of Genealogists and also of the journal for many years, finally ending her connection in 1967. There was a son by the first marriage. Blomfield died in 1948, aged 78 years, in harness as the editor of the journal.

Educated at University College School and Caius College, Cambridge, Blomfield completed his medical training at St George's Hospital. He qualified MB ChB in 1894 and MD in 1897. He was awarded the FFARCS in 1948. After house posts at St George's, he took up anaesthesia as a full-time career and joined the staff at a number of London hospitals, including St Mary's and the Grosvenor Hospital for Women and Children. But his main attachments were at St George's, where he remained on the staff until 1931, and the King Edward VII Hospital for Officers. In the latter post he seems to have been the principal anaesthetic adviser to Sister Agnes who ran the hospital as an autocrat.[9] He was commissioned into the Army in the First World War but served in London hospitals.

The Society of Anaesthetists and the Royal Society of Medicine

The society was founded in 1893 and elected Blomfield a member in 1900. He had two papers in the *Transactions of the Society*, in 1902 and 1903. He became Honorary Secretary in 1905. That was the time of the formation of the RSM, with the amalgamation of a number of specialist medical societies in London. But there were problems for anaesthetists: some were women but the RSM rules did not allow women to be admitted as fellows. Blomfield conducted the negotiations. By 1908, the society agreed to amalgamate with the RSM to become its anaesthetic section, and women could become fellows. The section, and the publication of its proceedings, were the main ways of propagating news about anaesthesia, although proceedings were usually summarized in the *Lancet* and the *British Medical Journal*. One of Blomfield's papers from the society appeared in full in the *Lancet* in 1902.[12] It discussed the problems of producing relaxation for abdominal surgery. It makes interesting reading. Remember that the anaesthetics available then were nitrous oxide, ether and chloroform. Many techniques involved substantial rebreathing and what we would now regard as dangerously hypoxic gas mixtures. Blomfield emphasized 'unimpeded breathing, complete absence of cyanosis and sufficiently deep anaesthesia'. Not a bad prescription, but he admits that success was not invariable. Blomfield became president of the Anaesthetic Section in the years 1911 to 1913 and vice-president from then until 1920.

In 1902 he also published a handbook of anaesthesia aimed at students and the occasional practitioner.[11] It ran to four editions, with the last appearing in 1917. The interval had seen the first practical moves towards intravenous anaesthesia, the use of resuscitation fluids, and the wider use of local anaesthetics. But his emphasis in all editions was on the three first anaesthetics: nitrous oxide, ether and chloroform. The techniques must have worked, but might not necessarily be accepted by examiners for the FRCA these days.

The Anaesthetic Committee of the Medical Research Council

Early in the 1920s, the council of the Anaesthetic Section of the RSM was receiving complaints that nitrous oxide was not working properly. There were also complaints that some brands of ether were not as effective as others, and even one that very pure ether was not an anaesthetic! At the same time, Henry Dale from the Medical Research Council (MRC) was worried that there was no professional body in the UK that would enable anaesthesia to catch up with work done in America and in Europe. As a consequence, the Joint Anaesthetic Committee was formed by the Anaesthetic Section and the MRC. The anaesthetists appointed were Blomfield, Francis Shipway from Guy's and Charles Hadfield from St Bartholomew's hospitals. The MRC fielded Dale, Professor Donnan from chemistry at University College, and Professor Pembrey, a physiologist from Guy's. All three were fellows of the Royal Society. Blomfield was elected chairman and Hadfield, secretary. The Committee lasted until 1948 and worked on the problems of nitrous oxide and ether, and on other anaesthetic gases and vapours, including ethylene, acetylene, propylene and cyclopropane. Mostly, the members of the committee did the work but they used outside experts such as Harold King at the MRC for the chemistry and Professor H. B. Dixon from Manchester when dealing with explosions. The committee persuaded the British Oxygen Company (BOC) to manufacture ethylene. Although it did not achieve much as an anaesthetic, ethylene was widely used elsewhere in the chemical industry. Imperial Chemical Industries (ICI) was also involved and set up a plant to make cyclopropane. The committee advised the British Pharmacopoeia Commission on the standards needed for medical nitrous oxide and other gases. Dale introduced other agents to the committee. Blomfield and Shipway pioneered the use of Avertin in the UK as a basal anaesthetic and published the results in 1929.[12] Blomfield wrote a short account[13] of one use for it: to anaesthetize a patient who would not consent to anaesthesia for an operation! In the 1930s, intravenous barbiturates were added to the armamentarium. The committee had access to hexobarbital (Evipan) and described its use in 1933.[14]

The committee also supported research by creating at least one fellowship. The MRC had been given an endowment to promote research in anaesthesia and analgesia. It managed to spend some, but by no means all, of the money. All the details can be found in the minutes books of the committee, which are stored in the Public Records Office at Kew. Towards the end of the 1930s, the committee had little to do and did not meet formally from 1938 to 1945. Anaesthetists were involved with research in the Second World War but not necessarily through this committee. Blomfield had a serious illness in 1945 and retired from the committee. Hadfield took over as chairman, with Geoffrey Organe as secretary.

The Association of Anaesthetists of Great Britain and Ireland

In the first issue of the journal, Cohen had asked for a national anaesthetic body for the UK. Although H.W. Featherstone was the prime mover in forming the AAGBI, Blomfield was a member of the provisional council in 1932 and elected the first vice-president at the inaugural meeting in 1933. Almost certainly, he wrote the welcoming annotation in the *Lancet*.[15] The association also pushed for a Diploma in Anaesthetics, and noted the problems for teachers of anaesthesia – do they please the surgeon, the patient or the trainee? It concluded with pleas for expert anaesthetists in all parts of the country and for due reward for their labours! Some things do not seem to change.

The journal published accounts of the annual meetings of the association and, at that time, Featherstone was a member of the editorial board of the journal. In 1935, Blomfield became president of the association until 1938 and he remained on its council until 1943. He was also the honorary secretary from 1939 to 1941. The first honorary secretary was Howard Jones of spinal anaesthesia fame who tragically committed suicide in 1935. There is an editorial[16] in the journal lamenting his passing and the reason for it – Jones could not make a living from anaesthesia, despite being one of the leading practitioners of his day.

What of the journal?

The journal continued its quarterly publication until the war years, when it came out only twice yearly until 1950. I counted some 255 papers, reviews and editorials in the 19 years under Blomfield. The topics were various and include political matters as to who should give anaesthesia for emergency surgery, and the problems of how anaesthetists should be trained. In 1937, the journal noted with pleasure the appointment of Robert Macintosh to the Nuffield Chair in Oxford.[17] The journal published the regulations for the Diploma in Anaesthetics when that was founded in 1935.

Despite the recession, anaesthesia and surgery were changing. R. J. Minnitt from Liverpool had joined the editorial board. The journal includes a description of his apparatus for the self-administration of nitrous oxide in obstetrics.[18] Obstetric anaesthesia and analgesia were continuing topics. In 1945, Crouch and Merry[19] published their account of epidural anaesthesia for Caesarean section. Papers came in from all round the world. Mortality and morbidity were frequent topics. The physiology of pain was discussed in 1937 by Leriche.[20] He makes many interesting points, particularly that chronic pain syndromes did not fit in well with the then current work on pain receptors and simple transmission systems through the peripheral nerves and main spinocortical pathways. The barbiturates appeared in the 1930s, with hexobarbital initially and later thiopental. Premedication, especially with atropine, had greatly reduced the problems of secretions. Oxygen was a great bonus. Curare made the first appearance in the journal for the neuromuscular blocking drugs in 1947.[21] Michael Nosworthy described his method of using cards to record anaesthetics and their outcome.[22] In 1945, E. Falkner Hill, a member of the editorial board since at least 1930, described the development of anaesthesia in the 45 years of his practice.[23]

Thoracic surgery was starting. Magill supplied a paper in 1936 on his technique for lobectomy.[24] The problems of the poor general condition of the patients were noted, as were those of avoiding the contamination of the healthy lung with the infected secretions of the damaged lobes. The paper discusses use of spinal anaesthesia that may sound strange to modern ears but also includes the use of bronchial blockers and selective intubation. In 1938 Haslar described his technique for one of the earliest forms of cardiac surgery – O'Shaughnessy's method of applying the omentum to the myocardium to relieve angina.[25] Following premedication, anaesthesia was induced with ethyl chloride and maintained with ether and oxygen. The problem of the open pneumothorax was dealt with by adding some 5–8 cm of positive end-expired pressure (PEEP) by placing the expired limb of the anaesthetic circuit under the appropriate water level. At the end of the operation, the lung was re-expanded by increasing the level of PEEP. In 1944, Philip Ayre described his technique for neurosurgery.[26] The breathing system employed the expected T-piece. Spinal anaesthesia was a popular topic. Howard Jones produced a splendid review in 1931 that detailed many of the myths and explanations of the technique.[27]

Death under, or associated with, anaesthesia was a common topic. Sykes in 1933 reviewed the results from a number of hospitals but was struck by the fallacy of small numbers and the problems of making comparisons.[28] From Melbourne, Green and Kaye[29] in 1934 noted that 'every anaesthetic fatality is made the subject of an enquiry' – an early foretaste of the Australasian interest in safety. In 1938, a lecture that Edwards from St George's Hospital had delivered to the medical students was reproduced.[30] It gives a splendid overall account of the problems.

The editorial board of the journal

There was a constant changing of the membership of the editorial board over the 25 years. Notable names at various times include: Dudley Buxton, Featherstone (the first president of the association), Magill, and Gillies from Edinburgh. But, at the end of the war, the journal was appearing only twice yearly, and there had been a suggestion of financial problems in the 1930s. The council of the association had made a grant to help keep it going. In 1945, Blomfield had his serious illness – he was 75 years old by then. Minnitt persuaded him to add some new members to the editorial board. T. Cecil Gray and R. P. (Jock) Harbord from Liverpool came on in 1948. The plan was to add other heads of departments in the several universities and medical schools in Great Britain.

Sadly, Blomfield died on 9 November 1948. His obituary appeared in the *BMJ*, *Anaesthesia*, the journal and in the *Lancet*. The latter[31] gives probably the best picture of him and his work. The penultimate paragraph is worth quoting almost in full: 'As an editorial contributor to our own columns, he was for many years a valued and entertaining colleague. In those relatively spacious times it was his habit to drop into the office after lunch, wearing a button-hole, smoking a cigar, and bearing a manuscript which could be deciphered only by the expert. (When he bought a typewriter the results were so remarkable that our printer begged him to return to the pen.) His notes on anaesthesia showed wit and judgement; and he was always prepared to write on other subjects, having a distinct journalistic talent as well as associations with Fleet Street. [. . .] He was, and remained, a companionable man, with a charm all his own.'

The editorial board of the journal needed to find a new editor.

Acknowledgements

I am most grateful to Dr Edmund Riding and the late Professor Andrew Hunter, who passed their files to me when they ceased being Honorary Treasurer and Chairman of the Board, respectively The libraries at the Royal Society of Medicine and the Universities of Southampton and Leeds gave access to the early issues of the journal and of the *Lancet*, the *BMJ* and the *Proceedings of the Royal Society of Medicine* The Public Records Office at Kew is a treasury with the old minutes of the Medical Research Council. The photographic section at the RSM undertook the copying of the two figures.

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British Journal of Anaesthesia **88** (3). 451–9 (2002)

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Air flow resistance of wet breathing system filters

Editor—The authors of a recent article in the *British Journal of Anaesthesia* proposed that our evaluations of heat and moisture exchanging filters (HMEF) for the Medical Devices Agency (MDA) should include a liquid challenge to determine the risk of device blockage.[1] They claimed that composite HMEF (filters with cellulose exchangers) are more likely to block than pleat only HMEF, and concluded that the results from a liquid challenge would provide clinicians with useful information when assessing the safety profile of individual devices.

We question how useful such information would be to a clinician. The worst-case scenario would be to add a large volume of viscous liquid (possibly KY Jelly™ would be appropriate) to the HMEF in a dependent position (so that the liquid collected on the filter surface). However, the usefulness of the result from such a test is unclear: hopefully only a tiny minority of HMEF used on patients in the ICU would be affected in this way, as most manufacturers of HMEF contraindicate the use of their devices in patients producing copious secretions. Clearly, it would be impossible to draft a specification in a standard for a 'liquid challenge' for HMEF intended to simulate a fault condition that had a useful and meaningful outcome.

Information on the moisture output, resistance to gas flow during normal clinical use and deadspace of an HMEF would be more useful when choosing between different devices. A review of the data on these variables for the three devices included in the study may lead to a different choice of device than the pleat only HMEF suggested by the authors.

The pleat only Pall BB22-15 has a comparatively low moisture output. A low moisture output will increase the viscosity of secretions in all patients, which may lead to blockage of the tracheal tube. It is, therefore, unlikely to be used in the ICU to provide humidification, whatever the result from a liquid challenge. (Pall market other devices that are more appropriate than this device.)

The International Standard for HME specifies that the pressure drop is measured across the device, both before and after the manufacturer's recommended period of use on a patient model.[2] The patient model 'expires' warm air fully saturated with water vapour, and condensation can and does collect within the device during the test period. The pressure drop measurements are therefore intended to represent those of the device in normal clinical use, when the device does, of course, get wet. The manufacturer is required to declare the pressure drop both before and after simulated use. The evaluation reports on HMEF published by the MDA include these data.

Unfortunately, the authors quoted the maximum limit for the pressure drop across HME of 5 cm H_2O from the first edition of the International Standard for HME, ISO 9360: 1992. This has been superseded by the second edition, published in 2000, which does not include this limit.[2] This change was made because the HME is just one component of the breathing system, and it is the resistance to gas flow of the whole breathing system that is important.

An HMEF with a large deadspace in relation to the patient's tidal volume increases rebreathing. The authors quoted the deadspace of the three devices that they investigated, but the values of 'deadspace' quoted in Table 1 of the paper are those of only the patient-side of the device. This may mislead some readers to think that these are the true deadspace values, in the absence of figures to the contrary. The 'true' deadspace is determined by measuring the pressure increase when a known volume is added to the sealed device. The figures for the deadspace from the MDA's evaluation reports for the Hygrobac S, Hygroster and BB22-15 (the three devices included in the study) are 49, 95 and 96 ml, respectively, compared to those quoted of 33.6, 56.6 and 53.8 ml, respectively. The smaller deadspace of the Hygrobac S may be considered to be an advantage over the BB22-15 in reducing rebreathing.

We would encourage vigilance with the use of these devices, as the use of HMEF is not without risk. In addition to the risk of blockage with secretions, blockage can also occur with inhalants.[3,4] Patients who are at risk of producing copious secretions and who are connected to an HMEF should be monitored closely. The authors claim that staff would notice secretions building up in the BB22-15 more easily than in the other two devices. However, vigilant staff should also notice changes to the pressure and flow waveforms due to an increase in resistance to gas flow from a build-up of 'inapparent' secretions and, when this occurs, the HMEF must be replaced. If this occurs frequently, then a heated humidifier should be used.[5] Nevertheless, an HMEF that has a low moisture output and an inappropriately large deadspace should not be used on patients receiving long-term ventilatory assistance, and the result of the proposed liquid challenge test is unlikely to change this conclusion.

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Editor—We would like to thank Wilkes and Stevens for their interest in our article. We wish to emphasize that we do not advocate the long-term use of breathing system filters in intensive care patients. The possibilities of increased work of breathing or even complete airway occlusion are major concerns for us. In the Sheffield Teaching Hospitals Trust, heated humidifiers are used for longer-term patients with filter use restricted to short-term ventilation.

We believe that the important properties of the ideal filter for use in the adult population are good moisture output, effective

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filtration and low resistance to air flow. These properties are potentially conflicting as our study demonstrates. Devices incorporating a cellulose heat exchanger could cause an increased work of breathing, or even device blockage, as a consequence of accumulation of excess condensation or patient secretions This is because wet cellulose expands and impedes airflow causing a 'tampon' effect. A variety of other heat exchange media exist and might perform differently in response to fluid challenge. For instance, a reticulated polyurethane foam impregnated with a hygroscopic additive would not be expected to expand when wet but would still provide good moisture retention. The performance of any heat exchange media will be influenced by the design of the device that incorporates it. For instance, a small device with a high relative cellulose content would be expected to produce a poor safety profile. The marginal increase in dead space associated with larger volume devices might be considered a price worth paying.

Wilkes' views on fluid challenge testing are a matter of record.[1] We do not agree with the statement that it would be impossible to draft a specification for a fluid challenge, indeed our simple test protocol might serve as a useful starting point. We agree that the vigilance of staff is an important element in the avoidance of breathing system filter blockage. However, multiple layers of protection are the ideal when it comes to averting adverse events.[2] The adoption of a standard designed to assess the risks of secretion-induced blockage would encourage the manufacture of devices with a superior safety profile should such a fault condition arise. The device that performed poorly in our testing is described by the Medical Devices Agency Evaluation report as 'a small HME and bacterial/viral filter which has an excellent performance with some good features'. Consideration of our data might lead the clinician to an alternative conclusion with respect to patient groups who are prone to secretion production.

Finally, we should mention that we presented our data to the British Standards Institute last year during the consultation phase for the forthcoming European standard for breathing system filters (BS EN 13328).

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Is xenon uptake in animals higher than reported previously?

Editor—In a recent article, eight pigs weighing 37.5–46 kg were anaesthetized with inspiratory xenon concentrations of 65%.[1] The xenon uptake was calculated by measuring the arteriovenous xenon concentration differences and using the Fick principle. The main finding was an uptake of 9977 ± 3607 ml (mean ± SD) of xenon during 2 h of anaesthesia. These findings are surprisingly high and do not correlate with our findings published previously.[2] Additionally, in a calculation using the computer program Narkup 4.11 (produced by Drs White and Lockwood, Northwick Park Hospital, London, UK) 120 min of anaesthesia resulted in a predicted body uptake of 4.01 litres in *humans* weighing 45 kg. We would like to discuss a few points with the authors·

i. Only a few valid gas chromatographic/mass spectrometric procedures which accurately measure xenon concentrations in blood are known to us and other groups studying xenon anaesthesia. The reason is the low blood/gas partition coefficient of 0.12 and high vapour pressure of 53 atm, leading to a rapid diffusion of xenon from blood samples.[3] The authors did not give any details as to how 14 blood samples per animal were withdrawn, processed and analyzed during the first 10 min of the experiment without any loss of xenon, nor how the analytical process has been validated. However, the results have a high standard deviation, suggesting that the authors experienced the same analytical difficulties as other groups.

ii. The Fick principle is intended to be used in steady state conditions. At time point 0 in the experiment, the application of xenon was started without denitrogenization. The measurements of arterial and mixed venous xenon concentrations were carried out simultaneously. The ventilator reached steady state conditions (inspiratory/expiratory xenon concentration differences of <5%) after 7 min of anaesthesia. Although the highest uptake of xenon occurs in the first minutes of anaesthesia, very low xenon concentraions were measured in venous blood, increasing the likelihood of errors. In addition, using dynamic conditions, time constants have to be taken into consideration when using the Fick principle. The authors did not change the animals from the ventilator used during induction and recovery to another ventilator, pre-filled with a xenon mixture in the desired concentration. By replacing only the amount of xenon which was taken up by the animals and lost by leakages minimization of measurement errors and steady state conditions from the beginning of the experiment could have been achieved.[4]

iii. The authors used diisopropylphenol in fatty solution (Propofol®) for an unspecified time during induction and surgical preparation of the animals, the recovery period of 2 h, and in the experimental period of 2 h of anaesthesia. Xenon has an oil/water partition coefficient of 20.[4] Infusing fatty solutions intravenously and simultaneously drawing blood samples, the venous blood possibly contains higher concentrations of triglycerides compared with arterial blood samples. Therefore a certain amount of xenon could have been dissolved in the fatty phase of venous blood, and not been available for analysis, further confounding the results. The authors did not report measurements of arteriovenous triglyceride concentration differences and correction of their results for these data. Why did they not choose to administer fat-free medication for anaesthesia?

iv. The experimental protocol (diffusion of xenon into prefilled and obstructed bowel segments), carried out simultaneously with the measurements could have increased the amount of xenon diffusing into the gut, thereby increasing total body uptake and influencing the results.

v. A rough validation of the experimental results could have been achieved by weighing the xenon bottles after the experiment. Did the authors weigh the bottles and was the amount of xenon usage (uptake+dead space of the ventilator+ventilator leakage) in the range calculated from measuring arteriovenous concentration differences?

Thomas Marx
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4 Marx T, Kotzerke J, Musati S, *et al.* Time constants of xenon elimination after anaesthesia. *Appl Cardiopulm Pathophys* 2000, **9**. 91–6

Editor—Thank you for the opportunity to comment on Dr Marx's letter. We are grateful for his interest in our study.

First, he points out that our determination of the xenon uptake in animals does not correlate with his own findings, and that he calculated lower values using the computer program, Narkup 4.11. Using a computer program to estimate uptake has weaknesses. There are different percentages of fatty tissue in different individuals. Intraluminal gas storage is not taken into account in computer calculations, which could be an important disadvantage (see point iv). The Narkup 4.11, requires many details about a patient, for example, sex, age, bodyweight, height, cardiac output, shunt fraction and functional residual capacity. The dead space of the ventilator, and for the different breathing systems, fresh gas flow, and minute volume are required. It demonstrates that, for instance, varying the cardiac output from 2 litre min^{-1} to 12 litre min^{-1}, the xenon uptake increases from 3.15 litre to 8.03 litre over 120 min of xenon anaesthesia. Furthermore, Narkup 4.11 uses a blood/gas partition coefficient of 0.14 for the calculation of xenon kinetics.[1]

In response to the points listed:

i. We agree with Dr Marx that it is difficult to measure xenon concentrations in blood directly. Nevertheless, an analytical method has been described for the determination of volatile compounds and gases in liquids some decades ago. Applying this approach, we used headspace gas chromatography/mass spectrometry (GC/MS) for the determination of xenon concentrations in blood. In headspace analysis, the analyte is measured in the gas phase (headspace) above the liquid in a closed vial and not in the liquid itself. The method is well known for the analysis of volatile compounds and gases in liquids. It is commonly used as a routine assay in environmental, petrochemical,[2] biochemical,[3,4] and forensic applications. Immediately after withdrawal, a defined amount of blood was transferred to a septum-capped headspace vial. After addition of internal standard, the vial can be stored for several hours or even overnight, but we performed the GC/MS analysis directly after the end of the experiment. Arterial and venous blood were withdrawn in parallel by different people. Sampling and processing within 10 min was not a problem.

The reported standard deviation reflects the biological variability and not the precision and accuracy of the analytical method. For the evalution of the method, we analysed two different venous blood samples which were withdrawn at 3 min and 30 min. For each sample we analysed eight different aliquots. The standard deviation was lower than 6%. To determine the precision of the method, known amounts of xenon were added to both samples. Again eight different aliquots were analysed. The standard deviation was below 4% and the difference between measured and calculated concentration was below 5%. The limit of detection was below $1\ \mu l$ Xe ml^{-1} blood.

ii. Dr Marx challenges the use of the Fick principle for non-steady state conditions. In its original form, the Fick equation is:

$$Cardiac\ output = \frac{oxygen\ consumption}{arteriovenous\ difference\ in\ O_2\ content}.$$

This estimation indeed fails if the measured oxygen consumption does not reflect oxidative use due to body retention or any other non steady state condition such as incomplete equilibration. The criticism raised by Dr Marx would apply if we tried to estimate cardiac output from xenon A–V differences and some measurement of xenon retention. However, we applied the Fick principle in the form:

$$\text{Body retention} = \text{cardiac output} \times \text{A–V difference}$$

This equation applies regardless of equilibration problems in the respirator. We calculated the body retention for each measurement interval considering the length of the interval, using the average concentration values for this interval, and a cardiac output value derived by thermodilution measurements. The sum of all intervals may not accurately reflect the true retention, but its approximation error cannot explain the differences mentioned by Dr Marx.

iii. We do not agree with Dr Marx's remark that the infusion of a lipid solution, in amounts described in our paper influences either the analysis or the xenon solubility in blood.

We determined the Ostwald coefficient of xenon in Propofol® (10% fat content) to be 0.35. Assuming that a pig weighing 40 kg has a total blood volume of approximately 3.2 litres and that there is no resorption of the fat administered (100 ml in 5 h), calculating the Ostwald coefficient as a weighted average of the solubilities in blood and the lipid emulsion respectively, showed that the Ostwald coefficient would only change from 0.115 to 0.122[5]. The value published in the literature was 0.14, 3 yr ago.[5] Consequently, infusing Propofol® had, at the most, a marginal influence on Xe solubility.

To examine if the analysis is influenced by different fat contents of the sample, we prepared calibration samples with water, blood, 10% lipid solution and original Disoprivan® 2%. Response ratios (xenon/internal standard) were plotted against amount ratios (xenon/internal standard) to obtain calibration graphs. The intercept of all calibration graphs was close to the origin and the slopes were 2.14 (water), 2.10 (blood), 2.29 (10% lipid) and 2.24 (Disoprivan®). Correlation coefficients were greater than 0.998. The minor changes in the slope of the calibration curve imply that a small lipid content does not influence the results.

iv. We agree with Dr Marx that diffusion of a significant volume of xenon into the intestine could occur during this experiment. After 4 h of xenon anaesthesia, we found a mean increase in the intestinal volume in a 50 cm segment of ileum of 40 ml. Assuming a total length of the small intestine of 10 m, an uptake of approximately 800 ml of xenon into the gut lumen is possible. Furthermore, uptake into fatty tissue may become important.

v. Taking into account that the weight of a 10 litre bottle of xenon is about 20 kg and the weight of 1 litre of xenon is 5.85 g, we agree with Marx that weighing a xenon bottle is only a rough validation to estimate the amount of xenon. This is underlined by Reinelt and co-workers, who reported problems during determination of the correct weight of xenon bottles during their experiments.[6]

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Measuring the cost of inhaled anaesthetics

Editor—In their paper on measuring the cost of inhaled anaesthetics, Drs Lockwood and White state that 'comparison between anaesthetics of the economies achievable has only been made by computer modelling' This is surprising.

As a regular user of low flow breathing systems, I ask myself:
i. how many ml of vapour min^{-1} am I using; and
ii. can I deliver the same amount with a lower fresh gas flow at a higher vaporizer setting?

The usefulness of expressing anaesthetic requirements in terms of ml of vapour used each minute has been demonstrated by Lin, Mostert and Benson.[2] The article, published over 20 yr ago, should be a classic reference for all low flow breathing system users. Lin and colleagues have demonstrated that, with a fresh gas flow of 500 ml min^{-1}, the requirements to maintian anaesthesia are 20 ml of vapour min^{-1} for halothane and 30 ml of vapour min^{-1} for enflurane, and that these requirements are remarkably constant.

Breath-by-breath monitoring, which is now available in operating theatres, reinforces this approach in clinical practice. The millilitres of vapour required to maintain anaesthesia with 500 ml min^{-1} fresh gas flow are 20–25 for isoflurane, 20–25 for sevoflurane, and 45–60 ml min^{-1} for desflurane. This is perhaps easier to demonstrate to a new trainee in spontaneously breathing patients, as the unaccounted leaks from a breathing system tend to be minimal and, if present, are usually in the expirating limb rather than from the inspirating limb as would be the case in artificially ventilated patients.

The comparative cost can then be calculated from the price we pay for a bottle of an agent and the number of grammolecules which the bottle contains.

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1 Lockwood GG, White DC. Measuring the cost of inhaled anaesthetics. *Br J Anaesth* 2001; **87**. 559–63
2 Lin CY, Mostert JW, Benson DW Closed circle systems. A new direction in the practice of anaesthesia. *Acta Anaesth Scand* 1980; **24**: 354–61

Editor—We thank Dr Zych for his interest in our paper,[1] which described the amount of anaesthetic that we would expect to be needed in a constant fresh gas flow into a circle system, in order to maintain a constant alveolar concentration We supported our claims in the cases of open and closed systems with measurements made on a number of patients during anaesthesia.

The work of Lin, Mostert and Benson[2] cited by Dr Zych describes a method of closed system anaesthesia: the volatile anaesthetic is included in the fresh gas during an initial 3 min period of high flow, after which the system is closed and the anaesthetic is delivered at a constant rate. The justification for a constant rate of anaesthetic delivery to the system is the 'near constant uptake of inhalational anesthetics across the alveolar membrane at a given inspired concentration', that is assumed to hold after wash-in to the functional residual capacity. Everything hinges on the word 'near', of course, and we have discussed this point elsewhere.[3] We accept that it is accurate enough for a rule-of-thumb for clinical practice, if the period of high flow is extended for 12 min, as in Lin's example case.[2] That illustration is the only evidence given to support the claimed halothane requirement, and no evidence whatsoever is given to support the calculation of enflurane requirement.

We therefore do not think that we have overstated our case when claiming that 'comparison between anaesthetics of the economies achievable has only been made by computer modelling', although we could have added that it is possible to draw conclusions from previously published opinions.

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Dexmedetomidine may be effective, but is it safe?

Editor—Venn and Grounds[1] have studied the autonomic and sedative effects of dexmedetomidine, in comparison with propofol, in a study of patients after major surgery. They judged the necessary size of their study in regard to the reduction in opioid given and heart rate reduction. They considered possible adverse events to be blood pressure values more than 40% away from baseline, bradycardia, tachyarrhythmia, and respiratory rates less than eight or greater than 25 min^{-1}. They conclude in their summary that this agent is safe and acceptable, and state on two occasions in the discussion that their study has shown that the agent is effective and safe. This is not a justifiable conclusion. Their study is only capable, with 95% confidence, of ruling out the risk of a rate of serious complications of 26%.

May I remind the authors, and their readers, of the aphorism and editorial 'If nothing goes wrong, is everything all right?',[2] which appears to have been ignored. The importance of this advice has been recently underlined by an editorial in *Anesthesiology*,[3] which reiterates some of the statistical faults of current scientific writing.

Venn and Grounds have conducted a study to demonstrate efficacy (in terms of reduced opioid dosage), not to establish safety. To claim to have done so, as they do, is untrue. An adequate safety study would need many more patients. For example, the accompanying editorial[4] cites the sorry tale of etomidate. Although this is perhaps a rather extreme example, it does remind us of how a large number of patients were given the agent before any lack of safety was discovered! I do not suggest that dexmedetomidine has the same effects, but the authors have not yet presented sufficient data to conclude that it is safe to use as an ICU sedative. If the authors were to report a study of 100 patients, without complication, then there would still remain a 5% possibility that the real complication rate could be as much as 3%.

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1 Venn RM, Grounds RM. Comparison between dexmedetomidine and propofol for sedation in the intensive care unit: patient and clinician perceptions. *Br J Anaesth* 2001; **87**: 684–90
2 Hanley JA, Lippman-Hand A If nothing goes wrong, is everything alll right? *JAMA* 1983; **249**: 1743–5
3 Todd MM Clincial research manuscripts in Anesthesiology. *Anesthesiology* 2001; **95**: 1051–3
4 Shelly MP Dexmedetomidine: a real innovation or more of the same? *Br J Anaesth* 2001; **87**· 677–8

Editor—Thank you for the opportunity to respond to Drummond's letter. He is correct in that this was a study to demonstrate efficacy and not safety, but with any new drug, reporting of adverse events is essential even if actual numbers studied are small. We commented in our discussion that dexmedetomidine appears to be a safe agent when interpreting data from this study *and previous work*.[1] A phase III study, which recruited from 36 centres in 11 countries, has reported on the safety of a continuous infusion of dexmedetomidine in 401 mechanically ventilated, postoperative patients in the ICU.[2 3] Our concern had been with the high incidence of cardiovascular adverse events (26% of patients recruited in the UK to the phase III study[2]), and consequently we reduced the loading infusion dose in this subsequent study.[1] No adverse cardiovascular events occurred with this reduction in dose, and as Drummond points out 'this study is capable, with 95% confidence, of ruling out the risk of a rate of serious complications of 26%'.

Thus we can be reasonably reassured that a reduction in the loading infusion dose of dexmedetomidine will prevent serious cardiovascular adverse events, as defined in our study.[1] However, this comes as no great surprise to any intensivist, since too much of any currently used sedative agent in the ICU may cause serious adverse cardiovascular events.

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1 Venn RM, Grounds RM. Comparison between dexmedetomidine and propofol for sedation in the intensive care unit: patient and clinician perceptions *Br J Anaesth* 2001; **87**· 684–90
2 Venn R, Bradshaw C, Spencer R, *et al.* Preliminary UK experience of dexmedetomidine, a novel agent for postoperative sedation in the intensive care unit. *Anaesthesia* 1999; **54**: 1136–42
3 Bachand RT, List W, Etropolski M, *et al.* A phase III study evaluating dexmedetomidine for sedation in postoperative patients. *Anesthesiology* 1999; **91**: A296

Remifentanil and pain relief in labour

Editor—We read with interest the article by Blair and colleagues[1] and would like to make some observations.

Even with its special features, remifentanil does not differ from other opioids, sharing their lack of effect in relieving labour pain.[2] In Blair's series, 38% of the women chose not to continue to use the PCA device. Is it appropriate to involve normal pregnant patients in a study using a treatment known to be inferior to other techniques (epidural or combined spinal epidural), especially if the latter are available at any time?

Roelants and colleagues[3] reported the use of remifentanil PCA in six patients in whom neuroaxial analgesia was considered contraindicated, and obtained adequate analgesia in four women; the other two underwent Caesarean section. We have only used remifentanil for pain relief in labour twice, in a patient with varicella infection and in a patient with severe thrombocytopenia. In both cases, a background infusion of 0.05 $\mu g\ kg^{-1}\ min^{-1}$ was used and boluses of 0.2 $\mu g\ kg^{-1}\ min^{-1}$ up to 1.0 $\mu g\ kg^{-1}\ min^{-1}$ as required, with supplementary oxygen and administration of metoclopramide and ranitidine.

We did not find a fall in arterial oxygen saturation below 90% and there were no abnormalities in the fetal heart rate. The median visual analogue score (VAS) was 4–5/10 with the best improvement obtained with concomitant use of entonox, when the VAS fell to 1/10.

We accept the safety profile of remifentanil in pregnant women,[4] and we agree with Blair and colleagues that remifentanil is the best opioid for systemic pain relief in labour, but we also think that it should only be offered when neuroaxial techniques are contraindicated.

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1 Blair JM, Hill DA, Fee JPH. Patient-controlled analgesia for labour using remifentanil: a feasibility study. *Br J Anaesth* 2001; **87**· 415–20
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4 Kan RE, Hughes SC, Rosen MA, Kessin C, Preston PG, Lobo EP. Intravenous remifentanil: placental transfer, maternal and neonatal effects. *Anesthesiology* 1998; **88**, 1467–74

Editor—We commend Blair and colleagues for their study of the use of remifentanil for analgesia in labour.[1] However, they fail to raise important concerns in their conclusions that merit closer scrutiny. We discontinued a preliminary study of manually administered remifentanil due to the significant side-effects encountered, and a lack of adequate pain relief with continued use.[2] Blair and colleagues demonstrated similar results. Despite increasing the dose of remifentanil, not only do they fail to get improved pain scores (level 2 and 3), but they also observed more adverse events. Twenty-five per cent of parturients had significant desaturation. Remifentanil was not continued to delivery in eight (nearly 40%) parturients. It is uncertain whether these patients would have experienced similar adverse events had they continued in the study. The combined effect of desaturation, sedation and reduced respiratory effort in an unmonitored mother seem disconcerting. Furthermore, they observed a significant number of episodes of vomiting, itching and dizziness (48%, 57% and 43%), as in our small study. Again, we need to ask whether these figures would have been higher had all their patients continued using remifentanil.

The multiparous benefited the most in their study and that at lower doses. We question whether their successes in these women were possibly due to the shorter labour duration. Unfortunately, they did not provide the duration of labour and thus the duration of remifentanil usage. We have observed brief improvement of pain scores on initiation of remifentanil boluses followed by a reduction of effect after 60–90 min. High pain scores at delivery,[1] similar to baseline pair scores, seem to suggest similar trends we had observed.[2] The development of tolerance to remifentanil may explain this observation.[3]

We believe that the incidence of adverse effects encountered is too high and cannot recommend remifentanil for routine labour analgesic use. Why should a drug that presents significant sedation and respiratory depression at low doses (level 1), and less pain relief at high doses with further side-effects (level 2 and 3) be recommended? In essence, if you are multiparous and unable to obtain an epidural, are able to tolerate vomiting, itching and/or dizziness, and able to accommodate the risk of significant desaturation episodes and near intolerable pain at delivery, remifentanil is for you!

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1 Blair JM, Hill DA, Fee JPH. Patient-controlled analgesia for labour using remifentanil: a feasibility study. *Br J Anaesth* 2001; **87**: 415–20
2 Olufolabi AJ, Booth JV, Wakeling HG, Glass PS, Penning DH, Reynolds JD. A preliminary investigation of remifentanil as a labor analgesic. *Anesth Analg* 2000; **91**: 606–8
3 Vinik HR, Kissin I. Rapid development of tolerance to analgesia during remifentanil infusion in humans. *Anesth Analg* 1998; **86**: 1307–11

Editor—We read with interest Arango-Arango and Restrepo-Garcés' experience with remifentanil for analgesia in labour. However, we would like to reassure them that the women who participated in our study had all stated a preference for opioid rather than regional analgesia. Indeed offering remifentanil only when neuroaxial techniques are contraindicated would, in our opinion, be denying patient choice in a population already motivated to use opioid analgesia.

We also thank Olufolabi and colleagues for sharing their experience with remifentanil. With regard to adverse events, it is important to emphasize that neither significant maternal desaturation or sedation occurred at our recommended dose (level 1). It is therefore erroneous to discount remifentanil on this basis.

Although 40% (eight women) did not continue remifentanil until delivery, the adverse events experienced by these women were actually included in the data. The decision in four women was precipitated by the need for instrumental or operative delivery; the remaining four women reported inadequate analgesia. The decision was not precipitated by adverse events.

The issue of tolerance to remifentanil has recently beeen questioned.[1] Although pain scores in our study did fall and subsequently rise again as delivery approached, this may reflect the fact that delivery is more painful rather than the development of opioid tolerance. It is likely that underdosing occurred at delivery, when the patients paid more attention to the midwife's instructions than the PCA button. In addition, the difficulties in reporting the changing severity and expectation of pain during labour may contribute.

The question of vomiting was detailed in our discussion. However, it is worth noting that at the recommended dose (level 1), nausea scores did not rise from pre-analgesia levels.

Finally, many of our patients commented on the benefit of remaining in control of their pain relief, something that was denied by the manual technique of Olufolabi and colleagues.[2]

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Howard Fee
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Tracheal cuff pressure—a survey of clinical practice

Editor—We were interested to read the survey by Spittle and Beavis,[1] demonstrating that only 13% of intensive care units (ICU) in the North West of England routinely monitor the cuff pressure of high-volume, low-pressure (HVLP) tracheal tube cuffs, and only 3% record the pressure on the patient charts. They correctly state that mucosal pressures cannot be guaranteed to be acceptable (less than 30 cm H_2O), as digital palpation of the pilot balloon is an unreliable indicator of cuff pressure. Excessive cuff pressures are related to tracheal injury,[2] and low cuff pressures may increase the rate of aspiration. The latter have been associated with an increased risk of ventilator-associated pneumonia.[3]

We did not have a cuff pressure measurement policy in the operating theatres or on the ICU, and so we conducted an audit of it in 30 sequentially anaesthetized patients and 30 sequential critically ill patients (cuff pressure checked once per patient). Neither the operating department practitioners who performed the cuff inflation in theatre nor the nurses in the ICU were aware that the audit was taking place. After recording the cuff pressure, it was normalized to 30 cm H_2O. If a leak was detected after reducing the cuff pressure, the cuff was re-inflated to just obtain a seal and the patient documented as having an appropriately high cuff pressure.

The mean cuff pressure for anaesthetized patients was 62 cm H_2O (range 20–120 cm H_2O, n=30). There were six (20%) cuffs with a cuff pressure above 100 cm H_2O. The mean cuff pressure for critically ill patients was 43 cm H_2O (15–105 cm H_2O, n=30). There were two cuffs (7%) that had a cuff pressure above 100 cm H_2O. Five patients had an approximately high cuff pressure (mean cuff pressure: 55 cm H_2O), as reducing it caused an audible air leak to occur.

We found that cuff pressures, and hence mucosal pressures, were often higher than recommended, frequently exceeding capillary perfusion pressure, and even on occasion exceeding systolic arterial pressure. We would recommend formal local protocols are used for cuff pressure measurement and maintenance and that the cuff pressure should be regularly recorded on the patient chart. Commercially available constant pressure cuff inflators have the advantage of continuous avoidance of low as well as high cuff pressure

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Editor—We thank Sathishkumar and Young for their interest in our survey. Their audit demonstrates that, without regular measurement, many ICU patients may have excessive tracheal cuff pressures. The impaired mucosal blood flow this causes can lead to life-threatening tracheal stenosis.[1] We disagree, however, that patients should have their cuff pressure labelled as 'appropriately high' if an air leak occurs on attempting to normalize it. It may be possible to reduce the cuff pressure required to avoid a leak by changing to a wider diameter tracheal tube, or changing the ventilatory mode to reduce the peak airway pressure.[2]

It is impossible to assess their data for anaesthetized patients, as they do not state whether these patients were intubated with high volume–low pressure cuffs, or whether nitrous oxide was used as part of the anaesthetic technique. The evidence of benefit in measuring tracheal cuff pressure in anaesthetized patients is less convincing than in ICU patients. As far as we are aware, the shortest period of tracheal intubation leading to a tracheal stenosis is 24 h.[3] Also, tracheal cuff pressure is probably not an important factor in the development of postoperative sore throat.[4]

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1 Spittle N, McCluskey A. Lesson of the week: Tracheal stenosis after intubation. *BMJ* 2000; **321**: 1000–2

2 Nightingale P, Clayton J. Intensive care services. In: Royal College of Anaesthetists Compendium, *Tracheal Tube Cuff Pressure. Raising the Standard.* 2000; Chapter 8, Audit 2

3 Yang KL. Tracheal stenosis after a brief intubation. *Anesth Analg* 1995; **80**: 625–7

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Evaluation of the Greenbaum sub-Tenon's block: a role in anticoagulated patients presenting for cataract surgery

Editor—I was interested to read Kumar and Dodds' paper[1] evaluating the Greenbaum sub-Tenon's block.

With reference to the use of diathermy as part of the technique, I recently practised in Australia, where pterygium (a condition where the conjunctiva are scarred from sun damage) is common. This condition made the performance of a sub-Tenon's block technically easier, reducing chemosis and subconjunctival haemorrhage, and increasing the speed of onset of the block. The final quality of akinesia and anaesthesia remained the same. The scarred tissue was less friable and easier to dissect, and it was possible to create a much narrower channel into the sub-Tenon's space with reduced retrograde loss of injectate. It would seem logical that the use of diathermy would reproduce such conditions, although I am not sure that anaesthetists would welcome using a diathermy probe so near to the eye.

I also note that the authors omitted to comment on the suitability of the sub-Tenon's technique in cataract surgery for anticoagulated patients. In a recent paper, Konstantatos[2] highlights the dilemma posed by anticoagulated patients undergoing cataract surgery. Prophylactic anticoagulation for atrial fibrillation or prosthetic cardiac valves is common in the age group presenting for cataract surgery, and there are significant risks arising from the cessation of such therapy. Koopmans and van Rij[3] reported that Dutch ophthalmologists stopped anticoagulation in 76% of patients undergoing cataract surgery and some severe systemic complications resulted, for example cerebrovascular events. They also noted that in those cases where anticoagulation was continued, ocular complications occurred, such as retrobulbar haemorrhage. They recommended continuing anticoagulation throughout the peroperative period and suggested that topical or sub-Tenon's anaesthesia could minimize the risks of bleeding.

The anaesthetic options for cataract surgery include general and local anaesthetic techniques; the latter can be divided into deep eye blocks, such as peribulbar and retrobulbar techniques, and the newer, more superficial techniques such as topical or sub-Tenon's block. Deep eye blocks are associated with the rare, but potentially catastrophic complication of retrobulbar haemorrhage. In anticoagulated patients, the incidence of clinically significant retrobulbar haemorrhage appears to be increased.[2]

Topical local anaesthesia, which is safer, has been facilitated by the newer extracapsular phacoemulsification techniques which appear to require less akinesia and a less dense sensory block, although Chittenden and colleagues[4] reported that topical anaesthesia produces suboptimal conditions for cataract surgery.

This leaves the sub-Tenon's block, which Stevens described as '. . . simple, reliable and offers excellent anaesthesia and akinesia whilst [it] avoids passing a sharp instrument into the orbit'.[5] Both Manners and Burton,[6] and Chittenden and colleagues,[4] highlights its advantages over topical techniques as it produces optimal akinesia and a dense sensory block comparable to deep eye blocks. Its advantages are repeatedly highlighted by others, including Stevens,[5] Manners and Burton,[6] and Guise.[7]

I have used the sub-Tenon's block effectively in anticoagulated patients presenting for cataract surgery without complication. The technique would appear to have significant advantages in these cases, which the authors did not mention.

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Editor—Thank you for the opportunity to reply to Dr Berrington. We have two separate comments.

The first relates to Dr Berrington's comments on diathermy. They are interesting, but I am not sure if they alter our view that anaesthetists are reluctant to use diathermy, period. An additional cause for concern with diathermy is that the only recorded perforation of the globe in delivering a sub-Tenon's block was when the operator (surgical) was performing the initial dissection. The scarring induced by diathermy could increase the risk of this complication.

We did not enter the debate on which regional orbital local anaesthetic technique is more or less appropriate in patients with a coagulopathy (iatrogenic or otherwise), as this should form a review article. To do justice to the topic an article would, as Dr Berrington has documented, need to cover a lot of ground. However, there is little doubt that current UK and USA ophthalmic anaesthetic opinion believes the sub-Tenon's approach to be the safest regional orbital local anaesthetic technique in patients on anti-coagulants.

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Simple height-based method of choosing the correct tracheal tube size in children

Editor—The variation in the size of children presents a problem for physicians in choosing the appropriate size of tracheal tube, especially in emergency situations.[1] Inaccuracy in choice is a greater problem than delay in making a choice.[1] It is vital that anaesthetists, emergency specialists and other physicians have a method for selecting the correct size of tracheal tube when confronted with a child for whom they have little or no clinical history

Methods of tracheal tube (ETT) selection based on anthropometrical data, such as height,[2–6] weight,[2] nares' size[6] and finger size,[5–7] exist. Estimates based on height provide the best correlation with correct tracheal tube size as determined by leak tests.[2–5] However, these height-based estimations require either a proprietary apparatus such as the Broselow tape,[3] or Pediatric Airway Management System™,[4] or complicated formulae such as, ETT size (mm)=2+(1/30×height (cm)),[5] or ETT size (Fr gauge)=(0.2×height (cm))+3.2.[6]

To investigate how trainees would respond to an emergency situation in which no clinical history was available about a paediatric patient, I conducted a survey of specialist registrars in anaesthesia doing their Paediatric Anaesthesia module. Three questions were asked. 1. How do you determine the diameter of tracheal tube to use for intubating the trachea of children? 2. How do you determine the diameter of a tracheal tube to use for a child for whom you have no history (age, weight, etc.)? 3. What other methods are you aware of for selection of the size of a tracheal tube in children, even if you do not use them? In scheduled cases in whom a full history was available, all trainees use an age-based formula. In answer to the second question, only 8/23 (34%) chose a method described in the literature, and 5/23 (21%) had no response. No specialist registrar was aware of any alternative method for choosing the size of tube, other than one based on age or little finger size.

A simple method of choosing tracheal tube size based on anthropometrical data is: ETT size (mm)=height (cm)/20. Eather and Turnbull, Attending Anesthesiologists, Children's Hospital and Medical Center, Seattle, USA devised this formula in the 1970s (personal communication). This formula has not been validated or published. To validate this formula, a prospective survey was conducted at Royal Manchester Children's Hospital on children aged less than 10 yr in whom the anaesthetist in charge decided to use an uncuffed tracheal tube during anaesthesia. The decision to intubate and choice of tracheal tube size were left to the anaesthetist. The correct size tube was considered to leak at a pressure of 10–30 cm H_2O and enabled adequate ventilation for a case. One consultant anaesthetist used ease of insertion and adequate ventilation as his end points for choice of tube size. For each child, age, height and tube size were recorded after intubation. The tracheal tube size chosen by the anaesthetist was correlated with three formulae: Age/4+4, Age/4+4.5 and height (cm)/20 cm. The first two formulae were those most mentioned in the survey of specialist registrars. Data were analysed using an SPSS package and Wilcoxon signed rank tests.

The total sample size was 52. The size of tracheal tube predicted by the formula, ETT size=Age/4+4, was not significantly different from the size deemed appropriate by the anaesthetist in charge (P=0.514). The size predicted by the formula, Age/4+4.5, predicted too large a tracheal tube ($P<0.001$). The size predicted by Height (cm)/20, also was not significantly different from the size deemed suitable by the anaesthetist in charge (P=0.288).

It appears that under controlled conditions in the operating theatre, the formula, ETT size (mm)=Height (cm)/20, accurately predicts the size of tracheal tube that the anaesthetist considers suitable for conduct of anaesthesia and is easier to use than other height-based formulae. It predicts ETT size with the same accuracy as the formula Age/4+4, but could be more convenient to use when the child's age is not known. Should a tape measure be unavailable, the average hand span is about 20 cm. This is supported by a survey of operating theatre staff at Royal Manchester Children's Hospital (male: n=20, mean=20.5 cm, SD=1.12; female: n=20, mean=19.1 cm, SD=1.01). The fact that standard tape measures are more readily available than Broselow tapes, makes this formula valuable in emergency intubation situations where history is minimal or age does not correspond to size. Since the average hand span is near 20 cm, the formula can be simplified to ETT size (mm)=height of child in hand spans. No formula, however, eliminates the need for a gentle intubating technique, and ready availability of a range of tracheal tube sizes to reduce the chance of failure or complications.

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Acknowledgement: The author would like to thank Dr R. Taylor PhD, Department of Biophysics, Hope Hospital, Salford, UK for assistance with statistical calculations.

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Mobile operating theatre in a district general hospital

Editor—The mobile operating theatre has been utilized in different countries for various purposes. It has been used during wartime to perform lifesaving procedures for a limited nature,[1] during renovation of the main operating theatre,[2] and to provide extra operating theatre sessions, to reduce waiting lists. A number of district general hospitals in the UK have used mobile operating theatres. At Burnley General Hospital this service has been utilized at least once a week, since September 2000, to provide two extra theatre sessions. Although the mobile operating theatre is not a new concept, and many anaesthetists and surgeons will be aware of it, they may not have used this commodity before. Few references regarding the mobile operating theatre are available. We wish to highlight the issues we encountered while working within this environment, which we feel are important when considering the use of the mobile operating theatre.

Patient and type of surgery

The mobile operating theatre is sited within the hospital compound, but it should be considered as an isolated unit and the selection of patients to be operated on in it should be more stringent.[3] Patients should be ASA I, ASA II, or well-controlled

ASA 3 patients. Very young children, if possible, should not be anaesthetized in such a setting.

The type of surgery performed in it should be day-case surgery It should not require complicated or additional equipment such as an image intensifier, or invasive monitoring devices such as transducers for central venous or pulmonary artery pressure measurement

Care must be taken during transport of patients to and from the mobile operaing theatre The unit should be situated as close as possible to the main hospital exit and some means should be provided along the pathway to the theatre (e g a canopy), to protect the patient from rain and other environmental hazards.

We have found that some patients are unaware that their operation is to take place in the mobile operating theatre, causing anxiety on arrival at the unit. Special consent should be considered from patients who are to be operated on in a mobile operating theatre.[2] Even if this is not mandatory, we feel that the situation should be explained to the patient, to ensure fully informed consent and to avoid confusion.

Medical and nursing staff

It is important to have regular medical and nursing staff who are familiar with the equipment and the environment within the unit, in order to ensure its smooth running. The list should be undertaken by more experienced senior surgeons and anaesthetists in order to prevent unnecessary complications, to reduce operating time, and to avoid any delay in the discharge of the patient from hospital.

Equipment and drugs

Although the mobile operating theatre comes equipped with its own facilities and nursing staff, the base Trust has to provide the surgical equipment and drugs. It is important that these items are available for a particular list or surgeon/anaesthetist.

From our experience, there have been a number of problems regarding this issue which have given cause for concern. First, there may be a lack of personnel immediately available to obtain equipment or drugs, particularly if the main operating theatre is some distance away This may result in a delay, or even cancellation of the procedure. Second, it is not possible or convenient to transport machinery to the mobile operating theatre. If a chest x-ray is required to exclude an intra-operative complication, it is not possible to bring the portable x-ray machine to the mobile operating theatre. This would necessitate the patient being moved from the mobile operating theatre to the main hospital for further investigation and management.

If equipment or drugs are to be stored in the unit overnight, the temperature of the unit should be kept constant, in order to avoid alteration of the drug's efficacy, or equipment malfunction.

Mobile operating theatre

The mobile theatre should be positioned at the same site every time it is utilized, so that other units and departments, particularly, the main switchboard, will be aware of its location The directions to the mobile operating theatre should be clearly displayed, so that it can be easily accessed in case of an emergency. Communication problems have occurred when the telephone line or the bleep system fails. Mobile phones have been used during an emergency, which is not ideal in the operating theatre environment. A back-up system should be provided.

These issues have been highlighted to ensure that all medical and nursing staff involved within mobile operating theatre units are aware of the differences between an ordinary operating theatre and a mobile one. The observations described should be taken into account for the safety of the patient, the smooth running of the operating list, and to avoid unneccessary cancellation of cases on the day of the surgery.

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J. Alfa
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1 Gasko OD. Surgery in the field during the Lebanon War, 1982: doctrine, experience and prospects for future changes *Isr J Med Sci* 1984; **20**: 350–4

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3 Ni KM, Watts JC Day case surgery in an isolated unit may require more stringent selection of cases *Anaesthesia* 2001; **56**: 485–6

Salim and Mahmood modification of RAE tubes

Editor—The RAE (Ring, Adair and Elwyn) tube has a preformed shape to fit the mouth or nose without kinking. It bends as the tube emerges from the mouth so that the connection to the breathing system is at the level of chin or forehead and does not interfere with surgical access. The RAE tube can be either south or north facing, cuffed or non-cuffed.

We are very satisfied with its use, but right and left sided tubes are not being manufactured It would be useful if the tube was angled at 90–120 degrees from its main axis (Fig 1) We have tried to shape the tube in a lateral direction and have used it successfully on our patients (the Salim and Mahmood modification of the RAE tube). Double fixation is advisable at the angle of the mouth and the angle of the mandible.

This will help to prevent pressure on the nose, eyes or forehead from the tube and the connector, especially in prolonged operations. With this modification it is also easier to maintain the airway when the patient is in the lateral position. The right or left fixation will give stability during transportation and allow Ambu bag ventilation in unconscious patients in the lateral position

We have used it in 25 cases during anaesthesia and transportation and found no complications with this design. We have recommended to the manufacturer that they produce right and left modifications of the RAE tube.

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Pakistan

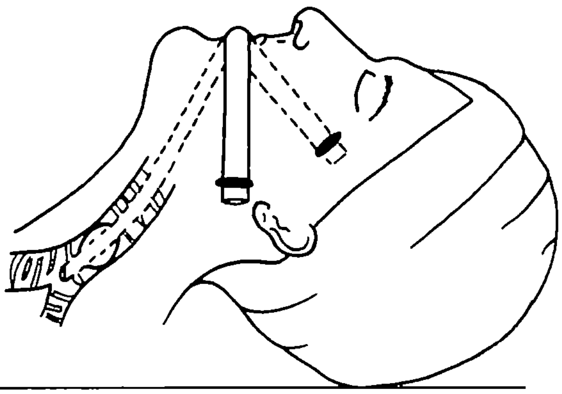

Fig 1 Modified left sided RAE tube moulded to an angle of 90° (solid line) and 120° (dashed lines)

British Journal of Anaesthesia 88 (3): 460–5 (2002)

Book Reviews

Topics in Neuroanaesthesia and Intensive Care. Georg E. Cold and Bent L. Dahl (editors). Published by Springer. Price £102.50. ISBN 3-540-41871-7.

The 12 topics in this book range from methods for measurement of cerebral blood flow to head injury management, aneurysmal subarachnoid haemorrhage, and the sitting position. In the preface, the editors suggest that the book was written not only for those with an interest in research relating to neuroanaesthesia and neurointensive care, but also to provide useful information for those whose daily practice encompasses such areas. In the first aim they have more than succeeded, but with the latter I tend to disagree.

As to the quality of the content, there is no doubt. The editors have tackled many enormous topics and condensed the important findings into manageable chapters. The longest chapter has only 47 pages of text and covers head injury from both experimental and clinical points of view, including guidelines for management from both sides of the Atlantic I found many important pieces of information here—but was a little frustrated over the lack of discussion, particularly concerning the Lund-management approach as compared with the more widely practised American approach. However, space is always at a premium and I cannot truly offer this frustration as a criticism, given the aim of the text. Another area I chose to follow-up was the vexed question of barbiturate use in head injury. There was a short section on this topic, but the question I am often asked by trainees 'how long between bursts is ideal in burst suppression' went unreferenced and unanswered.

I particularly enjoyed the chapter pulling together all the information on aneurysmal subarachnoid haemorrhage. Here the organization was good, moving through epidemiology and experimental models to the effects on intracranial pressure (ICP) and cerebral haemodynamics, with a long section on vasospasm and concluding with management principles. The chapters on anaesthetic agents were welcome and confirmed my preference for i.v. anaesthesia! It was also useful to have a chapter summarizing the use of vasoactive agents for either raising or lowering arterial blood pressure, and their effects on ICP and cerebral haemodynamics. However, I was a little surprised to find a brief introduction to G-protein coupled receptors (GPCRs) and G-proteins as the introduction to central α_2-agonists, giving the false impression that this transmembrane signalling system is unique to this receptor type. Many other GCPRs had been discussed prior to this point, without any reference to their molecular mechanism of action.

I must comment on the organization of the chapters. This was done in such a way that there were several levels of sub-headings, almost every paragraph had a heading. Although this extreme form of producing 'bite-sized' pieces of information seemed useful for some areas, in others it detracted from an overall view. The fragmentation often led to apparent contradictions in sentences from adjacent paragraphs. In some instances, this could be explained by re-examining the relevant sub-headings so that one statement had related, for example, to animal work and the other to human studies. In several cases though, contradictions were present. One example occurred in the chapter on head injury on p. 247, 'Hypocapnia improves cerebral autoregulation in the acute phase of head injury'. Yet on the same page, three paragraphs down, we are told '. . a decrease in Pa_{CO_2} does not improve CA in patients with HI' Such contradictory messages do not help the clinician who reads this book for information and guidance. This fragmented style is clearly suited to the researcher who can quickly identify the paragraph(s) relevant to their studies, but not a great help to clinicians trying to put the whole picture together. Despite such problems, the chapter on head injury is clearly full of useful references and would stimulate an inquiring mind to try and 'fill the gaps'.

One major criticism I do have is the very large numbers of references for each chapter. There are in excess of 1000 references for the chapter on ischaemia alone. Of the first 500 references, only 16% had been published in the last 5 yr, which increased only to 57% looking at those from 1990 onward. For a review of current ideas, I would have expected many references before 1990 to be excluded, as they will have appeared in earlier reviews. Did the editors really read all those thousands of references before writing the book? I just had to ask myself that question.

As a final personal comment, I was greatly looking forward to reading this text and learning from the editors' years of experience in the care of neurosciences patients. However, my enjoyment rapidly waned as the extremely poor proof reading and editing made reading some sentences a real challenge—even for a native English speaker. Although it is often charming to hear one's native tongue spoken with foreign grammatical structure it is a nightmare to try and read not only poor grammar but also poor spelling. The whole text suffered badly and the publishing house should be admonished for failing to get a native English speaker to correct the excessive number of errors. The title on the cover suggested that English spelling would be used throughout. This was not the case—even within a paragraph both English and American spellings of the same word were used. At a price in excess of £100, I would have expected better.

Nevertheless, I was impressed by the thoroughness of approach and will certainly dip again into the chapters on how anaesthetic agents alter cerebral blood flow, affect the intracranial pressure, and influence cerebral metabolism. I now have a source of information on which to modify or continue current practice in our neurosciences intensive care unit, and will point any potential researchers in the direction of this book; I am certainly pleased to have a copy for my unit! For trainees, however, I will suggest some lighter reading before they tackle it.

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Brain Edema XI. A.D. Mendelow, A. Baethmann, Z. Czernicki, J. T. Hoff, U. Ito, H. E. James, T. Kuroiwa, A. Marmarou, L. F. Marshall and H.-J. Reulen (editors). Published by Springer-Verlag Wein, New York. Pp. 572; indexed; illustrated. Price 167.80 Euros. ISBN 3-211-83561-X.

This book is the proceedings of the 11th International Symposium on Brain Oedema held in Newcastle-upon-Tyne in June 1999. It consists, therefore, of a collection of papers reporting clinical and experimental studies on cerebral oedema. The work reported in these papers is now more than 2 years old and it is likely that much of it has been published in peer-reviewed journals.

At the beginning of the book, there is a useful summary of the proceedings which states that the classification into cytotoxic and vasogenic oedema has been shown to stand the test of time and should continue to be used. There are sections on imaging, molecular mechanisms, cellular mechanisms, experimental studies/models, experimental ischaemia, pharmacology/therapy,

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head injury, head injury monitoring, stroke, subarachnoid haemorrhage and intracerebral haemorrhage, thermal effects, and hydrocephalus Each section is preceded by a useful summary of its contents written by the chairs of the sessions.

The sections on head injury and subarachnoid haemorrhage will be of interest to neurointensivists and neuroanaesthetists. In particular, the demonstration that prolonged isofluorane anaesthesia increases post-traumatic brain injury is of interest and raises the question as to whether other volatile anaesthetics have the same effect. However, there is very little of interest for anaesthetists and intensivists who are not involved in the management of neurotrauma in a neurosurgical unit, and much of the work reported is now a little old The book has a place in the libraries of neurosurgical units for reference purposes, but very few anaesthetists or intensivists are likely to purchase their own copies

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Video Review. Anaesthetic procedures—Carotid Endarterectomy. A. R. Bodenham. Published by Media Services, Leeds. Price £35.

This video is produced by Leeds General Infirmary to support the currently underway GALA trial (General Anaesthesia *vs* Local Anaesthesia for carotid endarterectomy (CEA)). It would appear from the title that this would be a detailed discussion of anaesthetic techniques for CEA; however, the title 'Anaesthetic and Surgical Techniques for Carotid Endarterectomy' appears as the opening credit. Even this is misleading and could have been written the other way around, since over half of the content is devoted to descriptions of two different surgical techniques for CEA in sufficient detail for the surgical Fellowship.

The video starts with an opening preamble about risk factors for developing carotid stenosis, followed by a passage about reducing risk perioperatively. Five factors are named as contributing to risk reduction during CEA (surgical technique, maintenance of cerebral perfusion pressure, shunt insertion, patch angioplasty, and use of local anaesthesia) No references are provided to support this however, whilst factors for which there appears to be some evidence were omitted (for example, surgeons performing more than 10 cases per year, preoperative cardiovascular optimization).

The meat of the video is discussion of two separate operations—standard CEA under general anaesthesia (GA), followed by eversion CEA under regional anaesthesia. The techniques used are perfectly acceptable, if a little didactic For example, routine central venous access for CEA under GA to allow administration of inotropes is hardly widespread practice. Some people would deliberately avoid it because of the risk of carotid artery damage, but this was got round by the use of ultrasonic localization of the internal jugular vein. It would have been good to have seen alternative (and perhaps more modern) anaesthetic techniques discussed. Whilst propofol or thiopental/fentanyl/vecuronium is traditional, many anaesthetists would nowadays use shorter acting drugs such as remifentanil, target-controlled propofol infusion, sevoflurane or desflurane together with a regional block to allow immediate neurological assessment postoperatively.

It was disappointing that anaesthetic *management* (as opposed to *technique*) was largely ignored. Monitoring deserves more attention—this patient population has a high incidence of ischaemic heart disease and the use of 5-lead ECG is more likely to detect myocardial ischaemia under general anaesthesia than standard 3-lead. Additionally, blood pressure monitoring—measurement in both arms, selection of allowable 'limits' during the case and selection of appropriate 'uppers' and 'downers', is not discussed No mention is made of other monitors of cerebral perfusion apart from Transcranial Doppler such as processed EEG, near infrared spectroscopy, and somatosensory evoked potentials.

I was most alarmed that the lady undergoing awake CEA did not appear to be receiving supplemental oxygen during the case—the video described how she was sedated with fentanyl and midazolam but then showed her with an oxygen saturation of 91% without a face mask This was a bad example to set for a teaching video Furthermore, the regional anaesthetic technique described (combined superficial and deep cervical plexus blocks) is perfectly adequate, but little attention is paid to complications of either blocks or their prevention. For example, the external jugular vein usually crosses sternocleidomastoid at exactly the point where one would want to do the superficial block; it needs to be avoided when injecting local anaesthetic, which is worth saying. Inadvertent injection of local anaesthetic into the vertebral artery or CSF is to be avoided at all costs during deep block (the video describes these complications as occurring 'occasionally'). However, the technique shown for injection of local anaesthetic does not minimize the chances of this happening. The 'immobile needle' technique in which one operator steadies the needle and syringe against the patient whilst a second operator aspirates and then injects, would have been better No mention is made at all of transient neurological dysfunction such as Horner's syndrome, recurrent laryngeal nerve palsy or phrenic nerve palsy which may accompany deep cervical plexus block. Patients with severe respiratory impairment may not tolerate the latter, which occurs in two-thirds of recipients of the block, so this group of patients should receive superficial block alone This is important information for prospective practitioners of this uncommonly performed block There was no discussion about choice of local anaesthetic or additives, except that the surgeon was given a very large amount of lidocaine (20 ml 1%) to administer perioperatively through a relatively large (21G) needle.

The surgical techniques were very clear and well described, including detailed descriptions of surgical instruments, choice of shunt and patch, and the relative merits of standard and eversion endarterectomy. Once again, the commentary was very didactic though, with comments like 'The carotid sinus nerve is blocked with local anaesthetic', which is controversially beneficial

I understand that this video was produced as a guide to surgeons and anaesthetists who may be randomizing patients to the GALA trial. However, surgical techniques are not being compared in this trial, so why were they given such prominence? After watching this video, a surgical trainee would understand many of the pitfalls and problems of carotid endarterectomy The same cannot be said for an anaesthetic trainee, who would receive little guidance about perioperative management or monitoring, together with the occasional 'howler' such as the lack of oxygen for the awake, sedated patient This video is an interesting introduction to carotid surgery, but it falls short of being a definitive anaesthetic guide

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Lung Volume Reduction Surgery. M. Argenianzo and M E Ginsburg (editors) Published by Humana Press, New Jersey. Pp. 273; indexed; illustrated Price US$145. ISBN 0896 03848-3

Lung volume reduction surgery is a fairy story for our time A 1950s idea, it was re-introduced in the last decade of the twentieth century for the surgery of emphysema as an alternative or, possibly, bridge to lung transplantation. Suddenly, here was the magic wand for a multitude of distressed and exhausted patients, dicing with death at the limits of their residual volumes Greedily, the wand was waved by surgeons. The result—the resources of medical insurance were consumed by their patients, languishing with big air leaks on intensive care units. Answer to this rather unedifying spectacle? A licensed, randomized, controlled trial of surgical *vs* medical treatment.

It is this book's misfortune to have arrived just as the results of this trial were published (*New England Journal of Medicine* 2001; **345**: 1075–83). The fable is now for a wider world and bestrides the Bristol enquiries in the UK. It, therefore, has to be examined by the microscope of the latter to tease out the lessons for the future scientific evaluation of surgical innovation. It is not my intent to digress from the book, but the recent publication is important. Suffice it to state that one of its most telling findings is that many of those who reluctantly found themselves assigned to the medical arm, may owe the randomization process their lives. In the end, the active arm effectively became the test bed for refining the criteria for those most likely to benefit from surgery.

I recall listening to Joel Cooper, the modern wizard of both lung transplantation and lung volume reduction. As he told his tale around the world, he emphasized the importance of the good fairy of anesthesiology to surgical innovation. You would not think so from this book. Interestingly, the specialty is not one of those mentioned in the preface for whom the book might be of interest. The chapters of interest to anaesthetists are neither practical nor scholarly. A return of self ventilation and early extubation, which drive the anaesthetic management and are the key to success, get little emphasis. Dynamic hyperinflation gets scant attention. There is little about its science or *modus operandi*, how to prevent it, spot its early signs, or treat it when it develops.

So where does this leave this book? Has it been undermined by events and spooked by anesthesiology? No, not completely, it is still a good treatise on the surgery of emphysema, not just lung volume reduction. It contains robust debates about the treatment options for emphysema which are germane both to thoracic disciplines and wider issues of surgical innovation in the twenty-first century. But, in particular, it is a tour de force as a record of the intellectual stardust and scholarship that as a consequence has invigorated the science of respiratory physiology. Here, some of the old truths, such as hypercarbia and hypoxic drive, are put away to bed. However, you do not need to buy a copy just for this, oustanding though it is; borrow it.

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Airway Management in the Critically Ill Rade B. Vukmir. Published by The Parthenon Publishing Group Ltd, Carnforth. Pp. 135; indexed; illustrated. Price £42.99. ISBN 1-84-214-046-9.

With increasing numbers of non-anaesthetists taking up training and consultant posts in intensive care, a book that deals principally with all aspects of airway management is certainly welcome. The stated aim of this book is to 'provide a structured framework to assess properly the needs of the critically ill patient in regards to emergency airway management'. It attempts to do this by covering all aspects of airway management over five chapters. The first deals with tracheal intubation, the second covers difficult tracheal intubation, and the remaining chapters are confirmation of tracheal tube placement, laryngotracheal injury from prolonged intubation, and surgical airway procedures.

Although chapter one is directed at the novice, it does not describe the procedure of intubation in any detail and the accompanying photographs are of poor quality. The description of anaesthesia is very brief and concentrates on the Guedel levels of anaesthesia which, with the modern armamentarium of drugs, has little relevance. The focus then switches to local anaesthesia of the airway and gives much discussion to the use of i.v. lidocaine. We are concerned that while it is not uncommon to use i.v. lidocaine to blunt the hypertensive response to intubation, its suggested use by this route as a method to achieve anaesthesia of the airway is both potentially dangerous and ineffective. Perhaps representing American practice, novices are encouraged to begin learning airway management using awake techniques, particularly focusing on blind nasal intubation. The majority of the chapter is dedicated to the pharmacology of various agents. Interestingly, only two paragraphs are given to propofol while three are provided for ketamine. Although muscle relaxants are discussed in detail, the focus is on the older, longer-acting agents including pancuronium and tubocurarine with only a small section on rocuronium. There are errors, for example in Table 1, where the indications and contraindications of tracheal intubation are reversed. Organization of the chapter is poor with aspiration precautions, premedication, cardiovascular sequelae, benzodiazepines, narcotics and barbiturates discussed under the heading of local anaesthetics. The final section covers a series of clinical scenarios which does give useful information for the choice of agents in particular disease states, but is not written for quick reference.

The second chapter looks at predicting, assessing and managing the difficult airway. The author covers the range of conditions that are likely to provide difficulties but does not offer any classification of these according to the nature of the problems likely to be encountered. There is a section on the various predictive tests which is well covered. The remaining section covers management strategies. This is effectively a detailed description of equipment, in particular the various laryngoscope blades, stylets and airway adjuncts. The limited information about techniques includes digital guided intubation, nasal intubation, oesophageal airways, fibreoptic intubation, retrograde intubation, percutaneous jet ventilation and cricothyroidotomy. Notably, there is little on the LMA† or methods of securing the airway *via* this device. The Intubating LMA is not mentioned and the technique of awake fibreoptic intubation, probably the mainstay of managing a number of difficult airway problems, is given little attention. The book does not provide the reader with the insight to devise a strategy for dealing with any particular airway difficulty that various conditions are likely to present. There is no classification, for example, as to which technique is best for managing a problem with soft tissues as opposed to bony abnormalities. The reader is not encouraged to have a plan B or C, and is left only with a long list of alternative laryngoscope blades that are probably not available in most hospitals.

The best, and probably most useful, chapter of the book is chapter four on laryngotracheal injury from prolonged intubation. Perhaps this represents the author's real passion as it reads well and offers some real insights into the problems associated with prolonged tracheal intubations, as well as suggestions for minimizing these effects.

Generally, we did not find the book easy to read. The numerous references disrupt the flow of the text and are generally old and full of statistics. The author has made no attempt to pull together the extensive research that has gone into the book, to offer conclusions and summaries that would fulfil the stated aim of providing information for generating intervention plans for airway management in the critically ill. It is quite easy to be overwhelmed by the information provided, and to feel confused as to how to specifically address a particular problem. The lack of organization within some chapters certainly makes quick reference more difficult. The photographs within the book are, at times, not referenced within the text. They lack adequate explanation and some have no accompanying key or legend. The area of interest has also been cut off in some cases!

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†LMA® is the property of Intavent Limited

Effective airway management is about having a primary plan and one or more back up plans in case this fails. We feel this book does not provide the means by which such plans can be quickly or clearly elucidated. Its recommendations regarding procedures that are rarely practised in the UK or Europe are misleading and the lack of organization or any firm conclusions leave the reader confused. Flexibility to take in all confounding variables is to be encouraged but the author has failed to establish even a broad framework within which to work. It is therefore difficult to recommend buying this book.

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International Anaesthesiology Clinics. Vol. 39: Number 3: 2001: *Medical Ethics.* Edward Lowenstein (editor). Published by Lippincott, Williams and Wilkins, Hagerstown. Pp. 148; indexed. Price US$74. ISSN 0020-5907

The subject of this edition of *International Anaesthesiology Clinics* is medical ethics The aim of the book is to present material of particular relevance to the anaesthetist, although the editor also hopes that it will be of interest to any physician. There are nine chapters in total, each written by a different author from the USA and each covering a separate topic.

Four of these chapters deal with life and death issues, and these will be of value to most anaesthetists with an interest in ethics. 'End of Life Issues in Surgery' is a general chapter written from the perspective of an anesthesiologist and gives an overview of ethical problems arising in anaesthetic practice. It includes both a discussion of the ethical issues surrounding a patient's demand for specific medical interventions, as well as the practice of withholding and withdrawing life support It contains a set of guidelines for the ethical practice of anesthesiology published by the American Society of Anesthesiologists (ASA) The withdrawal of life-sustaining treatment is dealt with in more detail in a separate chapter, which discusses both the ethical dilemmas and the practicalities involved with it. Cardiopulomonary resuscitation (CPR) is the subject of two chapters The first of these deals with 'Do not resuscitate' (DNR) orders and suggests a goal-centred approach to making such decisions. It also looks at the question of what should happen when a patient with a DNR order goes to the operating theatre. The second deals with the decision making process in CPR orders, and discusses whether it should be a medical one or a patient/surrogate choice It also looks at some of the issues surrounding autonomous decision-making and consent.

Other chapters of interest include one devoted to the subject of non heart-beating organ donation. This is a practice which occurs in very few centres within the UK, partly because of the surrounding ethical controversies Amongst those discussed are the conflicts of interest which arise when caring for dying patients who then become organ donors, and what constitutes an appropriate criterion for death determination in such cases. Finally, there is a chapter examining the problems posed by the uncooperative patient, which looks specifically at the ethics of coercion and constraint relating to patient consent. Using case histories it discusses how to deal with. the uncooperative patient in casualty; an elderly confused patient with a fractured neck of femur refusing surgery; and what to do with the uncooperative child presenting for surgery. These are situations in which most anaesthetists will find themselves at some time during their careers.

This leaves several chapters which are of less direct relevance to anaesthesia The first looks at the continuing evolution of bioethics in the USA since the Second World War, and suggests the need for more empirical research in this area. It is followed by a chapter that looks at the ethical issues surrounding the inherent conflict between the goals of science and those of medicine, as seen in Phase 1 cancer trials, and emphasizes the importance of gaining valid consent from patients enrolling in these trials Finally, with the financial imperative in the USA to cut costs in medical practice, there is a chapter discussing whether such cost-cutting activities fall within the established conditions of research. If they do, this would have implications for the need for informed consent before such activities are carried out.

This book is worth consideration if you have an interest in ethics. It is a book to be dipped into rather than to be read from cover to cover as each chapter deals with a discrete topic and is referenced Its main limitation is that it is heavily based on USA practice, where medical ethics has a much higher profile than at present within the UK; consequently, guidelines and legal advice are not always directly relevant to UK practice It does, however, stimulate the reader to reconsider certain ethical issues.

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Redditch

The Patient's Internet Handbook Robert Kiley and Elizabeth Graham. Published by Royal Society of Medicine Press Ltd, London. Pp. 302; indexed; illustrated. Price £9.95 ISBN 1-85315-489-9.

This short book aims to introduce patients and the general public to health information that is accessible through the Internet In particular, it seeks to guide patients to information sources that will help them to consult, on equal terms, with health professionals.

The book is divided into five sections. Section one consists of a general introduction to the Internet with basic, practical advice about connecting to it. Whilst this is pertinent for a complete novice it is unlikely that a reader without any Internet experience would be drawn to this book. Section two (Searching for Information) comprehensively describes different techniques used to search the Internet effectively. Different levels of searching are clearly explained including Boolean logic, the interrogation of databases, and the use of web directories and subject gateways Throughout this section, full use is made of illustrated examples including worked examples of search terms; the use of 'screen dumps' is very effective. The final chapter in this section focuses on discussion lists and newsgroups. Whilst the reader is warned that discussion lists and newsgroups 'epitomise the best and worst aspects of the Internet', and the reader is encouraged to discuss the findings of their Internet exploration with their doctor, an important piece of advice was omitted. Contributors to a discussion list frequently remain anonymous and the membership may include individuals with undeclared commercial (or other) interests

Section three features a selection of health topics. NHS services and the Internet are discussed along with drug information, complementary and alternative medicine, and pregnancy, childbirth and infant care. It is not clear why these subjects were chosen, other than that they are applicable to a general readership and indeed the information presented is wide ranging. A considerable proportion of the NHS services chapter is dedicated to hospital performance data, and debate about the paucity of information currently provided on the performance of individual doctors. Although the limitations of raw data are discussed in this section, the level of this debate is superficial. It is unlikely that reading this chapter would enable the lay reader to interpret the examples given.

Section four, 'Keeping Safe', offers valuable guidance regarding the evaluation of information derived from the Internet; however, despite the section title, only the first chapter concentrates on it. This important chapter contains helpful and instructive guidance and would perhaps have been better placed within Section two. The following chapter focuses clearly and helpfully on ways in which the reader can use the information gleaned from the Internet when consulting their doctor, and the final chapter addresses 'The Future'. This short but interesting section features developments in Internet technology including telemedicine, interactive health care, and the use of the Internet for continuing medical education.

The final section of the book is an extensive directory of health related websites with associated postal and telephone contact information. A brief description is given for each site along with details of any accompanying discussion list or newsgroups. The only reference within the book to anaesthesia was to the American Association of Nurse Anesthetists' website for information regarding the options for pain relief during labour; yet a basic search performed through the search engine Google found public information on web pages from the Royal College of Anaesthetists and the Association of Anaesthetists of Great Britain and Ireland.

The book is supported by a website (www.patient-handbook.co.uk), and the reader is advised to check this regularly or to subscribe to an email alert system for update information. However, this is a time-consuming endeavour for all concerned and may prove difficult to sustain; several websites that were suggested were not accessible, and this had not been updated on the website.

Overall, this book contained useful, valuable information and guidance, particularly the section advising patients on preparation for a medical consultation, but its purpose remained unclear. The website directory was potentially useful, but arguably superfluous given the detailed chapter on searching for information; likewise, for an example, the chapter concerning pregnancy, childbirth and infant care seemed unnecessarily long. In my experience, individuals wishing to obtain health information, particularly immediately following diagnosis, will want that information quickly and in a form that is readily understood. They will, therefore, turn to the medium with which they are most familiar. The scope of this book was too wide and would perhaps have been improved by assuming a certain level of Internet competence, and developing the theme of the 'empowered patient'. I would have difficulty recommending the book to any particular readership; novices are unlikely to use the Internet as their first choice for information, and regular 'surfers' would not require the level of detail provided in it

Helen Casstles
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Evidence Based Management—a Practical Guide for Health Professionals. Rosemary Stewart. Published by Radcliffe Medical Press. Price £18.95. ISBN 1-85775-4581.

Evidence-based medicine has been defined as 'the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients'. The strengthening of evidence-based clinical practice and consequent changes in disease management have led to calls for a similarly rigorous approach to the management of health care services and development of health policy.

This small book offers health service managers an insight into the techniques of evidence-based medicine. It sets out to show how the principles of finding and appraising evidence, developing organizations and individuals to use such evidence, and implementation of research can be applied to the management of services and to strategic decision making. Compared to medicine, the evidence base in management is relatively weak, but the author makes a strong case for seeking out and using objective evidence wherever possible. The case made, the focus of the book is on how to reduce obstacles to the practice of evidence-based management.

Concise and clearly written, each chapter highlights a separate aspect of implementation. These include self-management, the difference between information and knowledge, monitoring of services, making and implementing decisions, and—probably most importantly—the interplay between management styles, local organizational culture, politics, and the interpretation of evidence. Each topic is illustrated with a health-related vignette outlining an evidence-based management approach to stimulate reflection, and chapters close with a series of action-points for the reader.

To manage services effectively, we need to know whether we are doing the right things, and whether we are doing them as well as possible. Many managers will have been challenged to produce their evidence for a particular service change. Many clinicians, either moving into management roles or feeling the impact of changing services, will query the robustness of the underpinning logic when faced with change. Many, faced with stars (or no stars), traffic lights, or CHI visits, will want to critically appraise how well their current services are working, and to develop and deliver improvements. This thought-provoking book should help clinicians and managers to incorporate evidence-based strategies both when assessing whether they are doing the job right and, even more importantly, whether they are doing the right job.

Julia Moore
Wirral

Surgery, Sand and Saigon Tea. An Australian Army Doctor in Vietnam. Marshall Barr Published by Allun and Unwin. Price 27.20 Australian dollars. ISBN 1 865 084638.

It is only fair to point out that reading this book has evoked for me so many memories and reflections that, when it comes to drafting a review, it is proving very difficult to maintain any semblance of objectivity. The reason is quite simply that I followed in Marshall Barr's footsteps and, for 3 months in 1969, I worked as an anaesthetist at the same First Australian Field Hospital, Vung Tau, South Vietnam, as described by the author. Dr Barr describes it exactly as it was, not only how it was at the hospital, the work and the play, but also how it was to be in Vietnam at that time. I thought I had remembered it well but he has reminded me of so much more, the bits and pieces that are seemingly so easily forgotten. For me, the book is a postcard from the past, and one that I am delighted to have received and read. I hope I can do it justice

It all happened more than 30 yrs ago. The author is no longer the young personable anaesthetist who, at something of a loose end in Melbourne and disappointed in love, decided to have a shot at war. He volunteered for the Citizen Military Forces, and, with the Army eager to recruit specialist medical personnel for service with the Australian Taskforce in Vietnam he was, somewhat to his surprise, eagerly embraced by the Medical Directorate. As he writes, 'their welcome was flatteringly warm'. He was on his way, and the rest of the story is his.

It is a good story, honestly and engagingly told and with enough detail to satisfy any anaesthetist, young or old, with an interest in the 'difficult situation', particularly one with a military flavour. But there is more, a good deal more, than anaesthesia here.

The book is a sort of diary of perhaps the most interesting and challenging year of a life and, as it should be with a diary, the year is recounted with feeling and with candour, the latter not always necessarily to the author's credit. He indeed tells it as it was and, in doing so, spares himself no blushes. I liked him for that.

It is not a book for an anaesthetic department library. I am sure it was never meant to be so. Nor is it a book meant for anaesthetists, for anaesthetists only that is The author has made a point throughout of carefully explaining enough about anaesthesia and of anaesthetic paraphernalia to inform the lay reader, such that he or she will never feel lost. It is an easy and enjoyable book to read. I wonder, after so long, how easy and enjoyable it was to write. I had thought of having a go myself but, with Dr Barr having stolen the march on me, there is some comfort in the reflection that I no longer need to bother. Instead, I will defer certainly to the better man and probably to the better book

David Gray
Liverpool
UK

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Papers for publication and all editorial communications should be addressed to: Dr J. M. Hunter, Editor-in-Chief, *British Journal of Anaesthesia*, University Department of Anaesthesia, Royal Liverpool University Hospital, The Duncan Building, Daulby Street, Liverpool L69 3GA, UK. Tel./Fax: +44 (0) 151 706 4005. E-mail: bja@liv.ac.uk

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Methods
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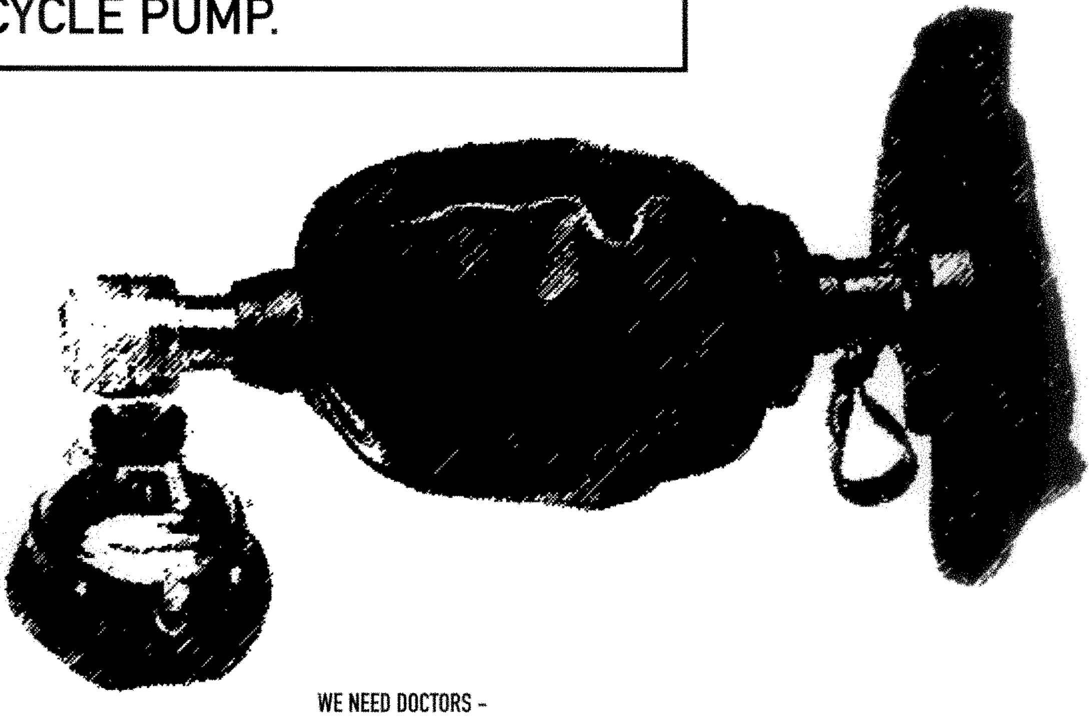

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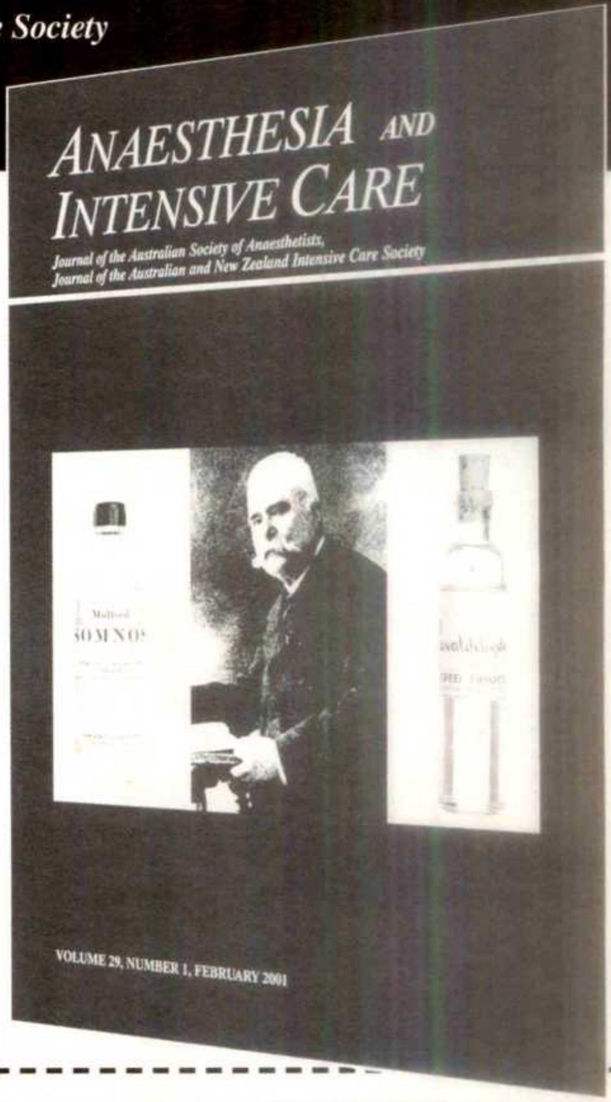

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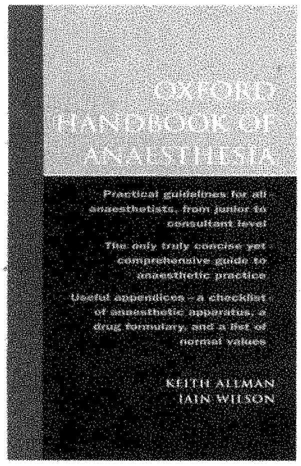

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Volume 88 Number 4 April 2002

EDITORIALS

467 I. Heparin resistance
J. A. M. Anderson and E. L. Saenko

470 II. Haemodilution enhances coagulation
T. G. Ruttman

473 III. 'Ventilating in recovery'—the way forward: intensive therapy or postoperative critical care?
A. G. Jones and S. J. Harper

CLINICAL INVESTIGATIONS

475 *In vivo* effect of haemodilution with saline on coagulation: a randomized controlled trial
K. F. J. Ng, C. C. K. Lam and L. C. Chan

481 Can a clinically useful aortic pressure wave be derived from a radial pressure wave?
S. Söderström, G. Nyberg, M. F. O'Rourke, J. Sellgren and J. Pontén

489 Glucose, insulin and potassium for heart protection during cardiac surgery
S. Bruemmer-Smith, M. S. Avidan, B. Harris, S. Sudan, R. Sherwood, J. B. Desai, F. Sutherland and J. Ponte

496 Dexamethasone decreases the pro- to anti-inflammatory cytokine ratio during cardiac surgery
S. R. El Azab, P. M. J. Rosseel, J. J. de Lange, A. B. J. Groeneveld, R. van Strik, E. M. van Wijk and G. J. Scheffer

502 Effect of sevoflurane/nitrous oxide *versus* propofol anaesthesia on somatosensory evoked potential monitoring of the spinal cord during surgery to correct scoliosis
A. S. W. Ku, Y. Hu, M. G. Irwin, B. Chow, S. Gunawardene, E. E. Tan and K. D. K. Luk

508 Malignant hyperthermia associated with exercise-induced rhabdomyolysis or congenital abnormalities and a novel *RYR1* mutation in New Zealand and Australian pedigrees
M. Davis, R. Brown, A. Dickson, H. Horton, D. James, N. Laing, R. Marston, M. Norgate, D. Perlman, N. Pollock and K. Stowell

516 Comparison of mepivacaine and lidocaine for intravenous regional anaesthesia: pharmacokinetic study and clinical correlation
P. Prieto-Álvarez, A. Calas-Guerra, J. Fuentes-Bellido, E. Martínez-Verdera, A. Benet-Català and J. P. Lorenzo-Foz

520 Effect of perioperative administration of dexketoprofen on opioid requirements and inflammatory response following elective hip arthroplasty
G. Iohom, M. Walsh, G. Higgins and G. Shorten

527 Randomized crossover comparison of the ProSeal with the classic laryngeal mask airway in unparalysed anaesthetized patients
T. M. Cook, J. P. Nolan, C. Verghese, P. J. Strube, M. Lees, J. M. Millar and P. J. F. Baskett

534 The ProSeal laryngeal mask: results of a descriptive trial with experience of 300 cases
N. R. Evans, S. V. Gardner, M. F. M. James, J. A. King, P. Roux, P. Bennett, R. Nattrass, R. Llewellyn and D. Visu

LABORATORY INVESTIGATIONS

540 Increased airway resistance during xenon anaesthesia in pigs is attributed to physical properties of the gas
J.-H. Baumert, M. Reyle-Hahn, K. Hecker, R. Tenbrinck, R. Kuhlen and R. Rossaint

546 Xenon increases total body oxygen consumption during isoflurane anaesthesia in dogs
O. Picker, A. W. Schindler, L. A. Schwarte, B. Preckel, W. Schlack, T. W. L. Scheeren and V. Thämer

555 Does ester hydrolysis change the *in vitro* degradation rate of cisatracurium and atracurium?
M. Weindlmayr-Goettel, H. Gilly and H. G. Kress

REVIEW ARTICLE

563 Chirality: a blueprint for the future
D. Burke and D. J. Henderson

SHORT COMMUNICATIONS

577 The postanaesthesia care unit as a temporary admission location due to intensive care and ward overflow
A. Ziser, M. Alkobi, R. Markovits and B. Rozenberg

580 Radial artery cannulation: topical amethocaine gel *versus* lidocaine infiltration
S. J. Olday, R. Walpole and J. Y. Y. Wang

582 Postoperative sore throat after ambulatory surgery
P. P. Higgins, F. Chung and G. Mezei

584 ProSeal laryngeal mask protects against aspiration of fluid in the pharynx
N. R. Evans, S. V. Gardner and M. F. M. James

587 No evidence of mutations in the *CACNA1S* gene in the UK malignant hyperthermia population
C. Brooks, R. L. Robinson, P. J. Halsall and P. M. Hopkins

CASE REPORTS

590 Transoesophageal echocardiographic monitoring of pulmonary venous obstruction induced by sternotomy closure during infant heart transplantation
C.-P. Lin, K.-C. Chan, Y.-M. Chou, M.-J. Wang and S.-K. Tsai

592 Oesophagotracheal perforation after intraoperative transoesophageal echocardiography in cardiac surgery
J.-B. Lecharny, I. Philip and J.-P. Depoix

595 Late oesophageal perforation after intraoperative transoesophageal echocardiography
M. P. Zalunardo, D. Bimmler, U. C. Grob, R. Stocker, T. Pasch and D. R. Spahn

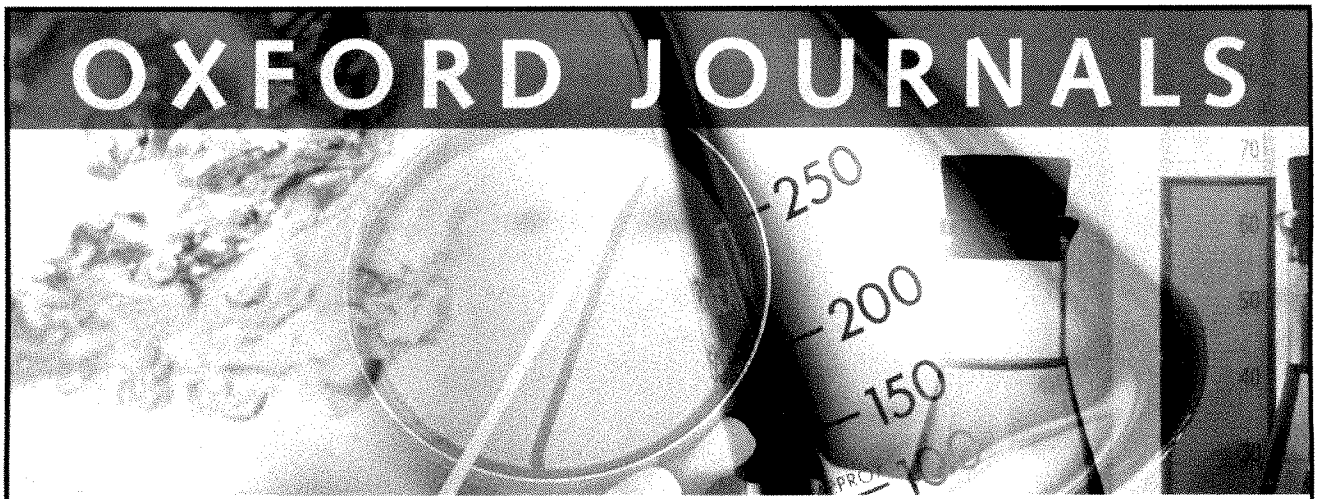
597 Oxygen embolism after hydrogen peroxide irrigation of a vulvar abscess
G. Haller, E. Faltin-Traub, D. Faltin and C. Kern

600 Anaphylaxis to rocuronium
C. Baillard, A. M. Korinek, V. Galanton, Y. Le Manach, P. Larmignat, M. Cupa and C. M. Samama

603 CORRESPONDENCE

615 BOOK REVIEWS

619 ERRATUM



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BJA/RCA RESEARCH FELLOWSHIPS and GRANTS

The *British Journal of Anaesthesia, in conjunction with the Royal College of Anaesthetists* is making a further round of grants available to support research in anaesthesia, intensive care or pain relief.

Project Grants are available to support specific research in anaesthetic departments. Joint applications with basic science departments will be welcome. These grants may be awarded to fund technical staff, research students or post-doctoral research fellows; salaries, or items of equipment. The maximum value of any award will be £50 000, and the *BJA/RCA* will not contribute towards overheads.

The *BJA/RCA* will also consider funding **Research Fellowships** with this round of awards. Applicants should note that candidates will usually be members of academic departments of anaesthesia; and the grant must be administered by an academic department of anaesthesia and have the support of the head of that department.

For further details and forms, please **write** or **Email** to: Dr J. W. Sear (BJA Grants Officer), Nuffield Department of Anaesthetics, University of Oxford, John Radclife Hospital, Headington, Oxford OX3 9DU *or* john.sear@nda.ox.ac.uk

Closing date for applications is **April 30th, 2002**. Late applications will **not** be considered.

Final FRCA Revision Course

Leicester Royal Infirmary, April 8–11, 2002

An intensive revision course for the Final FRCA based on small group tutorials and including written and oral examination practice.

Fees: £290 including lunch and refreshments; £335 with 3 nights accommodation; £350 with 4 nights accommodation. Places are strictly limited.
For a booking form, please contact: Christine Gethins. Tel: +44 (0)116 258 5291; Email: anae@le.ac.uk.

Advances in Minimally Invasive Hand/Upper Extremity Surgery

Genval (Brussels), Belgium, April 19–20, 2002

The symposium will promote exchange between scientists and clinicians, and will include presentations by invited faculty. Participants may submit original papers for a limited number of oral presentations, and there will be considerable time reserved for discussion. Deadline for submission of abstracts: December 31, 2001.

For further details, please contact: F. Schuind, MD, PhD, Department of Orthopaedics, Erasme University Hospital, 808 route de Lennik, B-1070 Brussels, Belgium. Tel: +32 2 555 68 44/36 45; Fax: +32 2 520 35 56: Email: fschuind@ulb.ac.be

Artificial Oxygen-carriers: a Clinical Future?

The Royal College of Physicians of Edinburgh, Edinburgh, May 9, 2002

Speakers to include Dr John Hess, Professor Donat Spalm, Dr J. Maguire and Dr Dafydd Thomas. With contributions from the major companies attending a prior workshop.

For further details, please visit the website: http://www.rcpe.ac.uk/AOCs or Tel: +44 (0)131 225 7324; Fax: +44 (0)131 220 4393

Putting New Flesh on Old Bones: a major conference on Issues in the Perioperative Care of Geriatric Trauma

The Netherwood Hotel, Grange-Over-Sands, UK, May 10, 2002

Speakers include: Nigel Sharrock (New York); Martyn Parker (Peterborough)

Deadline for free paper abstracts: February 1, 2002.

Please contact Dr Andrew Severn for details: Tel: +44 (0)1524 583517; Fax: +44 (0)1524 583519.

Australian and New Zealand College of Anaesthetists Annual Meeting

Brisbane Convention and Exhibition Centre, Brisbane, Australia, May 11–15, 2002

For further information please contact:

ANZCA 2002 Secretariat, PO Box 1280, Milton QLD 4064, Australia.

Tel: +61 (0) 7 3858 5537; Fax: +61 (0) 7 3858 5510;
E-mail: anzca2002@im.com.au; Website: www.anzca.edu.au

Royal Australasian College of Surgeons and The Royal College of Surgeons of Edinburgh, Annual Scientific Congress

Adelaide, Australia, May 11–15, 2002

A joint meeting of the colleges to celebrate the 75th anniversary of the Australasian College. A team of speakers will address: Clinical Governance, Quality in Surgical Education, Remote and Rural Surgery, Medical Legal Problems, Colorectal Surgery, Paediatric Surgery, and Trauma.

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Registration for Fellows of the Royal College of Surgeons of Edinburgh will be through this College. Please contact: Mrs Maureen Lowrie in the Education Section of the College. Tel: +44 (0)131 668 9209; Fax: +44 (0)131 668 9241. Email: m.lowrie@rcsed.ac.uk

Annual Symposium Sedation Teaching: Problems and Solutions

Royal College of Physicians, Regent's Park, London, May 14, 2002

The group provides a forum for everyone who is interested in the teaching of conscious sedation in dentistry. Members include dental or medical practitioners and nurses from university, hospital, community and general practice backgrounds.

The themes of the 2002 symposium are education, new sedation techniques and DSTG initiatives; the standard teaching document and logbook will be presented.

John Lowry, President of the Royal College of Surgeons will describe the role of the Royal College of Surgeons in sedation training. Practical aspects of teaching sedation to undergraduates and postgraduates will be discussed.

Symposium venue: The Royal College of Physicians, 11 St Andrews Place, Regent's Park, London, UK (www.rcplondon.ac.uk).

Registration: members £85; non members £95 (cheques payable to DSTG Symposium). The meeting is open to DSTG members and non-members. Eligible non-members will be offered one years free membership.

For further information please contact: Carole Boyle, Floor 26, Guys Dental Hospital, London Bridge, London SE1 9RT, UK. Email: carole.boyle@kcl.ac.uk.

First World Congress on Regional Anaesthesia and Pain Therapy

Barcelona, Spain, June 5–8, 2002

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; Email: dionne@options.com.cy

12th Meeting of the Liver Intensive Care Group of Europe (LICAGE)

Barcelona, Auditorium Winterthur, June 6–8, 2002

This meeting will include three symposia: 'Expanding the liver pool', 'Renal abnormalities in the liver peri-transplant period, mechanisms, management and prognosis', and 'MARS in the management of severe hepatic insufficiency', two lectures: HepatAssist clinical trial on fulminant hepatic failure: final results' (M. Muraca, Padova) and 'Cerebral oedema in liver diseases: its importance in the management of the peri-transplant period' (A. Blei, Chicago), and a joint conference on 'Controversies in the management of acute liver failure' (J. Bernuau, Paris and J. Wendon, London). There will also be oral communications and poster presentations.

Scientific information: Dr Antoni Mas, Servicio de Hepatologia, Dra. Pilar Taurá, Servicio de Anestesiologia, Hospital Clinic, Villarroel 170, Barcelona 08036, Spain. Tel: +34 93 227 54 99; Fax: +34 93 451 55 22; Email: amas@medicina.ub.es (Dr Mas), ptaura@clinic.ub.es (Dra Taura)

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Ralph M. Waters, MD, and Professionalism in Anesthesiology: A Celebration of 75 years

The Concourse Hotel & Governor's Club, Madison, Wisconsin, USA, June 6–8, 2002

A combined meeting of Anesthesia History Association (US) and History of Anaesthesia Society (Great Britain) with additional sponsors: University of Wisconsin Medical School, Department of Anesthesiology and Office of Continuing Medical Education, Wisconsin Society of Anesthesiologists, and Wood Library-Museum of Anesthesiology. This conference will celebrate the arrival of Ralph M. Waters, MD, in Madison, Wisconsin, in 1927, and explore his legacy in anaesthesia practice and professionalism. Abstracts are invited on any aspect of his career and legacy and also on any aspect of anaesthesia history related to the three broad areas of professionalism to which Dr Waters contributed: (1) education; (2) research; and (3) creation of specialty societies designed to promote improvements in the clinical and ethical standards of practice in anaesthesiology. Abstract deadline: March 1, 2002.

Conference information: Mark E. Schroeder, MD, Associate Professor, Department of Anesthesiology, University of Wisconsin Medical School, 600 Highland Avenue, Room B6/319, Madison, WI 53792-3272, USA. Tel: +1 608 203 8105; Fax: +1 608 262 6247; Email: aha2002@anesthesia.wisc.edu; website: http://www.anes.uab.edu/anehist/watersconf.htm

XVIth Edinburgh Anaesthesia Festival

Edinburgh, UK, August 21–23, 2002

A three-day programme consisting of lectures and discussion on current topics in anaesthesia.

For further details, please contact: University Department of Anaesthesia, Critical Care and Pain Medicine, Royal Infirmary, Lauriston Place, Edinburgh EH3 9YW, UK. Tel: +44 (0)131 536 3652; Fax: +44 (0)131 536 3672. Email: anaes@ed.ac.uk

Anaesthesia outside the square: CECANZ Conference 2002

Christchurch, New Zealand, September 18–20, 2002

For information, please contact: Conference Secretariat Joy Mehlhopt, Conference Innovators, P.O. Box 1370, Christchurch, New Zealand.

Tel: +61 3 379 0390; Fax: +61 3 379 0460; E-mail: joy@conference.co.nz. Website: www.cecanz2002.org.nz

Past, Present and Future of Jet Ventilation: Symposium and Workshop together with 2nd Annual Meeting and General Assembly of the European Society for Jet Ventilation

Friedrich Schiller University, Jena, Germany, September 20–21, 2002

For further information please contact: Mrs Marina Wolf, Department of Anaesthesiology and Intensive Care Medicine, Friedrich Schiller University Hospital, Bachstr. 18, D-07740 Jena, Germany. Tel: +49 3641 933642; Fax: +49 3641 933448; Email: kongress.kai@med.uni-jena.de; Website: http://www.med.uni-jena.de/anaesthesie

Société Française d'Anesthésie et de Réanimation

Annual congresses will take place in Palais des Congrés, Porte Maillot, Paris on the following dates:

September 26–29, 2002
September 18–21, 2003
September 20–October 3, 2004
September 29–October 2, 2005

For further information, please contact: SFAR, 74, rue Raynouard, F-75016 Paris, France. Tel: +33 1 45 25 82 25; Fax: +33 1 40 50 35 22; E-mail SFAR@invivo.edu

Dingle 2002—4th Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 2–6, 2002

For further information contact: Dr Monty Mythen, Director, Centre for Anaesthesia, UCL, Room 103, 1st Floor Crosspiece, Middlesex Hospital, London, W1T 3AA, London, UK. Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com

Australian Society of Anaesthetists National Scientific Congress

Adelaide, Australia, October 26–30, 2002

This is the Society's premier scientific conference, held in an interesting part of the world.

For further details, please contact: Festival City Conventions, P.O. Box 949, Kent Town, S.A. 5071, Australia. Tel: +61 (0)8 8363 1307; Fax: +61 (0)8 8363 1604: E-mail: asa2002@fccconventions.com.au

8th International Congress of Cardiothoracic and Vascular Anesthesia
19th International Congress of the Israel Society of Anesthesiologists

Jerusalem, Israel, November 10–13, 2002

For further information regarding the Congress, please contact:
8th International Congress of Cardiothoracic and Vascular Anesthesia, PO Box 50006, Tel Aviv 61500, Israel

Tel: +972 3 5140000; Fax: +972 3 5140077; E-mail: anesth2002@kenes.com

Web address: http://www.isranest.org.il/congress 2002

German Congress of Anaesthesiology 2002 (DAK 2002)

Messezentrum Nürnberg, June 26–29, 2002

German Congress of Anaesthesiology 2003

(DAK 2003)
Messezentrum Nürnberg, June 18–21, 2003

For further information, please contact:

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Tel: +49 911 393160; Fax: +49 911 331204

International Anaesthesia Research Society Annual Clinical and Scientific Congresses

March 22–26, 2003
IARS 77th Clinical and Scientific Congress, New Orleans Marriott, New Orleans, Louisiana, USA.

March 27–31, 2004
IARS 78th Clinical and Scientific Congress, Tampa Marriott Waterside Hotel, Tampa, Florida, USA.

27th Congress of The Scandinavian Society of Anaesthesiology and Intensive Care Medicine

Helsinki, Finland, August 16–20, 2003

A biannually arranged Scandinavian congress in one of the five Scandinavian countries; language: English.

For further information please contact: Prof. Per H.Rosenberg, Helsinki University Hospital, Helsinki FIN00029 HUS, Finland.

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PRECAUTIONS

Consider monitoring renal function in patients with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis. Use caution when initiating treatment in patients with considerable dehydration. Rehydrate patients prior to starting therapy with rofecoxib. Consider the possibility of fluid retention and exercise caution when rofecoxib is used in patients with pre-existing oedema, a history of heart failure, left ventricular dysfunction or hypertension. Maintain appropriate supervision when treating the elderly or patients with renal, hepatic or cardiac dysfunction with rofecoxib. Rofecoxib may mask fever. Use of rofecoxib is not recommended in women attempting to conceive. In clinical studies, some osteoarthritis (OA) patients treated with rofecoxib developed perforations, ulcers or bleeds (PUBs). Patients with a prior history of a PUB and patients greater than 65 years of age appeared to be at a higher risk for a PUB. At chronic daily doses higher than 25 mg, the risks of gastro-intestinal symptoms, oedema or hypertension are increased. Elevations of ALT and/or AST (≥3 times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with rofecoxib. Any patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated. *Interactions (pharmacodynamic): Warfarin:* closely monitor the prothrombin time INR when therapy with
rofecoxib is initiated or changed in patients receiving warfarin or similar agents, particulai
first few days. *ACE-inhibitors:* administration of 25 mg daily of rofecoxib with benazepri
to 40 mg daily for four weeks to patients with hypertension was associated with a small att
of the antihypertensive effect compared to the ACE inhibitor alone. This should be consi
patients taking rofecoxib concomitantly with ACE inhibitors. *Beta-blockers and diuretics:* con
use of NSAIDS may reduce the antihypertensive efficacy of beta-blockers and diuretics and
effects of diuretics. *Aspirin:* at steady state, rofecoxib 50 mg once daily had no effect on
platelet activity of low-dose (81 mg once daily) aspirin. Avoid concomitant administration of r
with higher doses of aspirin or other NSAIDS. *Cyclosporin/tacrolimus:* monitor renal functi
rofecoxib and either cyclosporin or tacrolimus is used in combination. *Interactions (pharmaco*
Lithium: NSAIDS may increase plasma lithium concentrations. *Methotrexate:* consider
monitoring for methotrexate-related toxicity when rofecoxib and methotrexate are adm
concomitantly. *CYP1A2 substrates:* exercise care with concomitant administration of rofecc
drugs primarily metabolised by CYP1A2 (e.g. theophylline, amitriptyline, tacrine and z
Midazolam: a modest 30% reduction of the AUC of midazolam was seen with rofecoxib 25 r
most likely due to increased first pass metabolism through induction of intestinal CYP3A4
by rofecoxib. *CYP3A4 substrates:* in spite of a modest induction of intestinal CYP3A4 acti
pharmacokinetics of drugs metabolised primarily by CYP3A4 are not expected to be affec
clinically significant extent. However exercise care when co-prescribing substrates of CYP3

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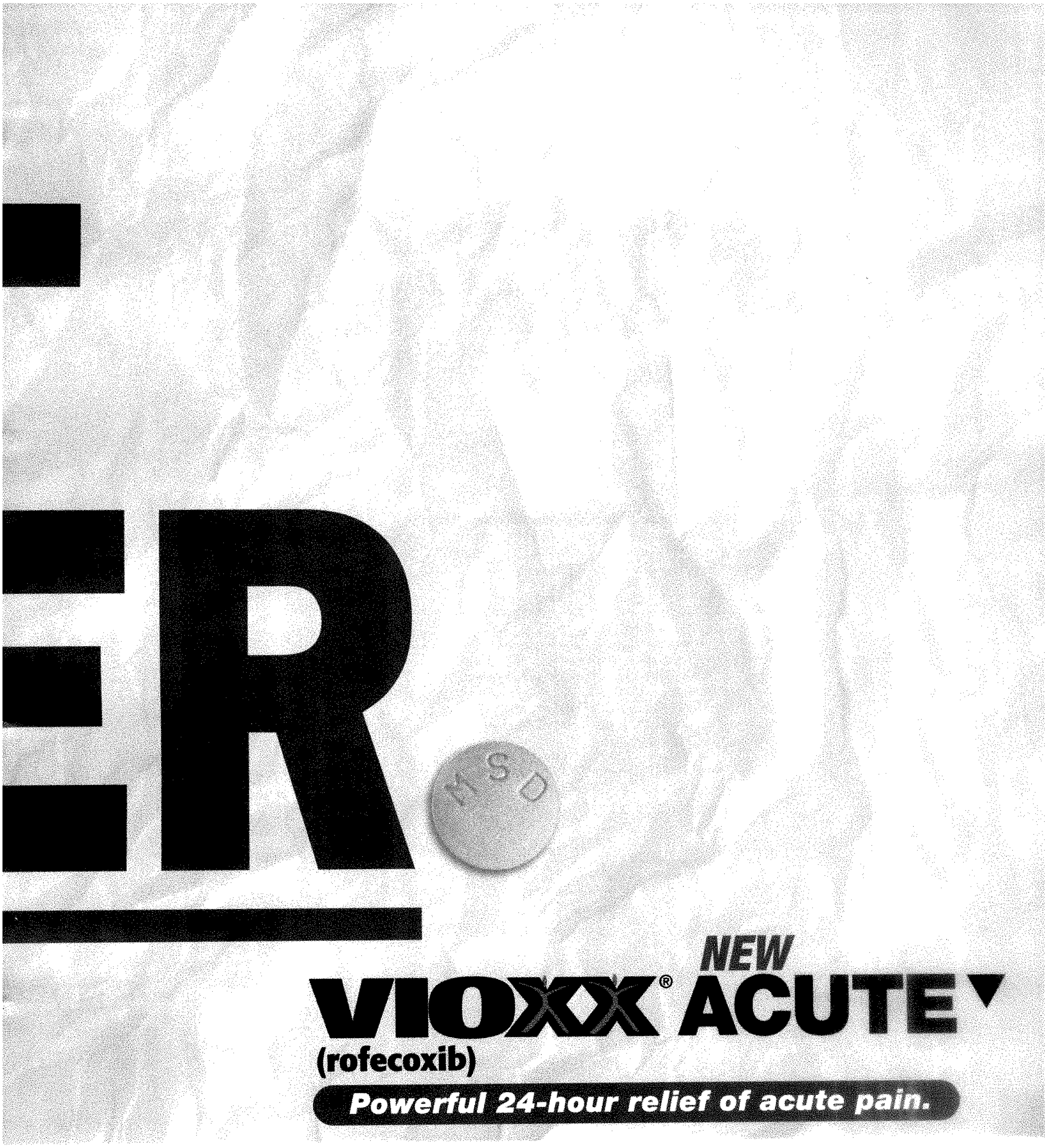

Rifampicin: co-administration of rofecoxib with rifampicin, a potent inducer of CYP roduced an approximate 50% decrease in rofecoxib plasma concentrations. Therefore, e highest dose when rofecoxib is used with potent inducers of hepatic metabolism. Based data, rofecoxib is not expected to inhibit cytochromes P450, 2C9, 2C19, 2D6 or 2E1. : Do not use in the last trimester of pregnancy, because like other prostaglandin synthesis ofecoxib may cause uterine inertia and premature closure of the ductus arteriosus. Rofecoxib be used during the first two trimesters of pregnancy unless the benefit to the patient the risk to the foetus. *Lactation:* contra-indicated.

ECTS

ng drug-related undesirable effects were reported at an incidence greater than 1% and n placebo in analgesia clinical studies in patients treated with rofecoxib 50 mg or 25 mg ays: dizziness, diarrhoea, diaphoresis, dyspepsia. The following drug-related undesirable e reported at an incidence greater than placebo in osteoarthritis clinical studies in patients th rofecoxib 12.5 mg or 25 mg for up to six months, or in post-marketing experience. *(≥1/100, <1/10); Uncommon (≥1/1000, <1/100); Rare (≥1/10,000, <1/1000); Very 0,000) and isolated cases]*

whole/site unspecified: *Common:* oedema/fluid retention, abdominal pain, dizziness. n: asthenia/fatigue, abdominal distension, chest pain. *Very rare:* hypersensitivity reactions, ngioedema, urticaria and anaphylactic/ anaphylactoid reactions. ***Blood and the lymphatic system disorders:*** *Common:* haematocrit decreased. *Uncommon:* haemoglobin decreased, erythrocytes decreased, leukocytes decreased. *Very rare:* thrombocytopenia. ***Cardiovascular system:*** *Common:* hypertension. *Very rare:* congestive heart failure. ***Digestive system:*** *Common:* heartburn, epigastric discomfort, diarrhoea, nausea, dyspepsia. *Uncommon:* constipation, oral ulcer, vomiting, digestive gas symptoms, acid reflux. *Rare:* peptic ulcers, gastro-intestinal perforation and bleeding (mainly in elderly patients), gastritis. ***Hepatobiliary disorders:*** *Common:* alanine aminotransferase increased, aspartate aminotransferase increased. *Uncommon:* alkaline phosphatase increased. *Isolated cases:* hepatotoxicity including hepatitis and jaundice. ***Eyes, ears, nose and throat:*** *Uncommon:* tinnitus. *Very rare:* blurred vision. ***Metabolism and nutrition:*** *Uncommon:* weight gain. ***Musculoskeletal:*** *Uncommon:* muscular cramp. ***Nervous system:*** *Common:* headache. *Uncommon:* insomnia, somnolence, vertigo. *Very rare:* paraesthesia. *Isolated cases:* aseptic meningitis. ***Psychiatric disorder:*** *Uncommon:* depression, mental acuity decreased. *Very rare:* confusion, hallucinations. ***Respiratory system:*** *Uncommon:* dyspnoea. *Very rare:* bronchospasm. ***Urogenital:*** *Uncommon:* BUN increased, serum creatinine increased, proteinuria. *Very rare:* renal insufficiency, including renal failure, usually reversible upon discontinuation of therapy. ***Skin and skin appendages:*** *Common:* pruritus. *Uncommon:* rash, atopic dermatitis. *Very rare:* alopecia. *Isolated cases:* cutaneo-mucosal adverse effects and severe skin reactions including Stevens-Johnson Syndrome. In clinical studies, the undesirable effects profile was similar in patients treated with rofecoxib for one year or longer. The following serious adverse effects have been reported in association with the use of NSAIDs and cannot be ruled out for rofecoxib: nephrotoxicity including interstitial nephritis and nephrotic syndrome; hepatotoxicity including hepatic failure.

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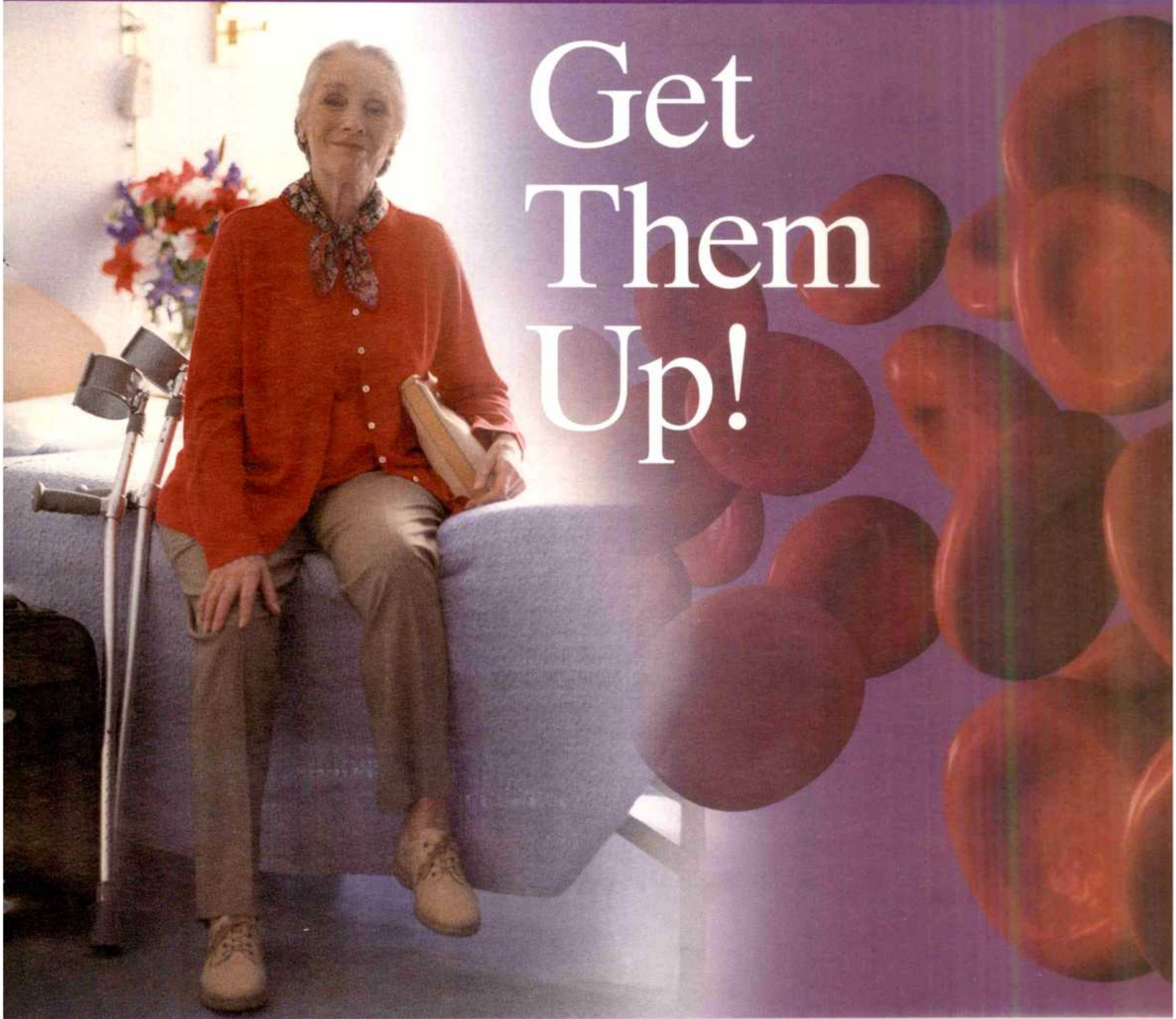

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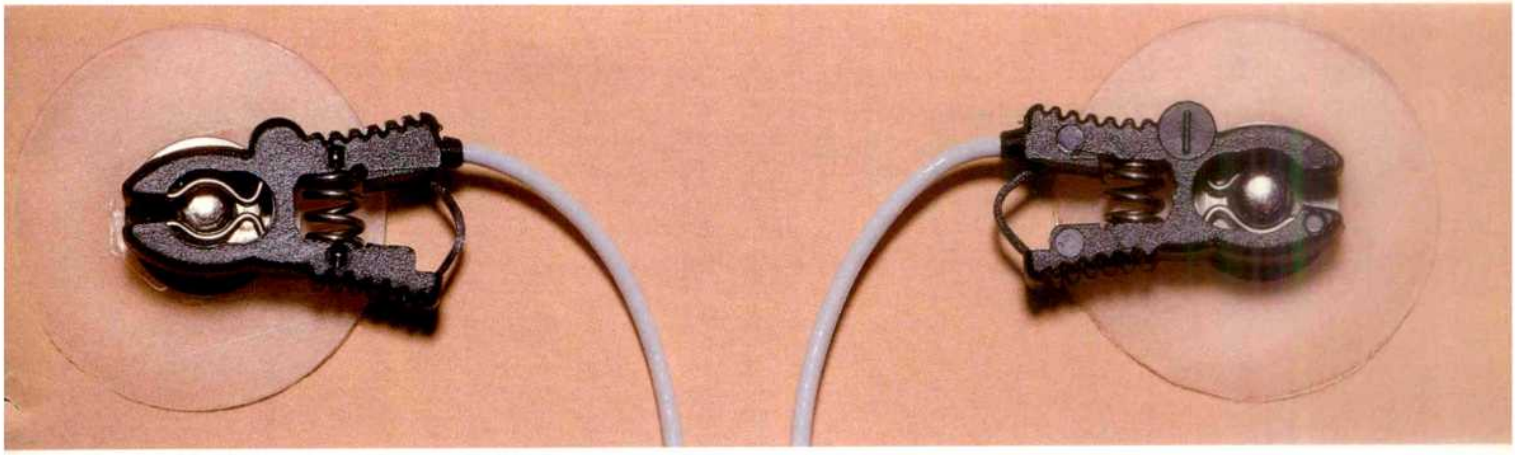

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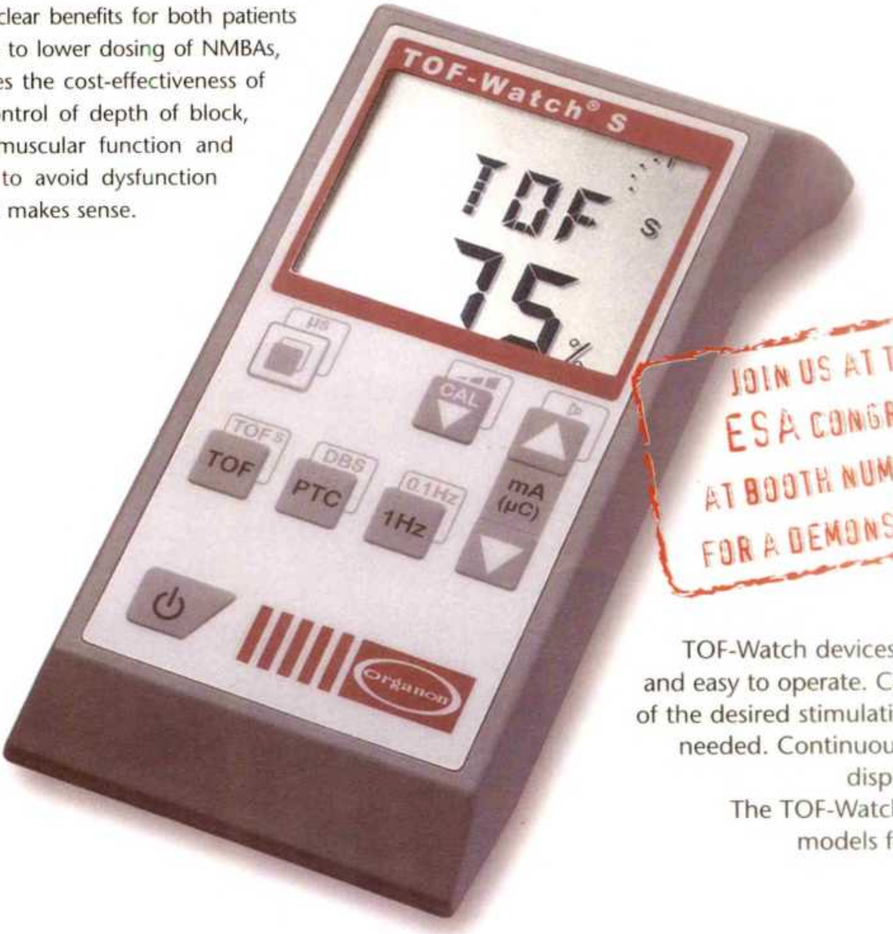

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Editorial I

Heparin resistance

Heparin was discovered at the beginning of the twentieth century by McLean (1916).[1] Twenty years later (1936) its chemical structure was accredited to the Swedish chemist Jorpes.[2] Sixty-five years on it is the most widely used anticoagulant, but are all its actions fully understood? How does it achieve pain relief when administered intravenously for the treatment of overt deep venous thrombosis? Why do some recipients develop heparin-associated thrombocytopenia, and what is the relevance of the occurrence of heparin resistance?

Heparin is a negatively charged, sulphated glycosaminoglycan, composed of alternating uronic and glucuronic acid residues. Commercial preparations are isolated from porcine intestinal mucosa or bovine lung, and are heterogeneous mixtures of polysaccharide chains ranging in molecular weight from 3000 to 30 000, with a mean molecular weight of 15 000.[3] Heparin principally exerts its anticoagulant effect by activating antithrombin (AT); the heparin-antithrombin (H-AT) complex then inactivates thrombin, activated factor X (fXa) and other activated clotting factors.[4] A unique combination of disaccharide units makes up the critical pentasaccharide sequence containing the high affinity binding site for antithrombin. This sequence occurs in only about one third of heparin chains and is randomly distributed.

In purified systems, heparin and low molecular weight heparin (LMWH) have been shown to have AT-independent effects on blood coagulation by the direct inhibition of the intrinsic tenase (X-ase) complex, a phospholipid membrane complex of activated factor VIII in association with activated factor IX which generates fXa.[5] In plasma milieu, the AT-dependent effect predominates.

The clinical effectiveness of heparin is dependent on achieving an *in vitro* defined anticoagulant effect, although there is considerable *in vivo* variation in response to a fixed dose of heparin between individuals. This is partly reflective of the pharmacokinetic limitations of heparin, caused by the binding of heparin to plasma proteins,[6] in addition to the problems encountered in measuring its desired anticoagulant effect. These add to create a phenomenon known as 'heparin resistance', which should be taken into consideration to prevent the over-administration of heparin, with potential haemorrhagic consequences, particularly post-operatively and in the setting of cardiac bypass surgery. In the treatment of venous thromboembolism the phenomenon is of unclear clinical significance.

In the context of venous thromboembolism, heparin resistance is defined as the need for more than 35 000 U 24 h^{-1} to prolong the activated partial thromboplastin time (APTT) into the therapeutic range. In contrast, during cardiac bypass procedures, the definition of heparin resistance is based on the activated clotting time (ACT), with at least one ACT less than 400 s after heparinization and/or the need for exogenous antithrombin administration

What causes heparin resistance, and which patient groups are susceptible? This question can be answered by understanding some of the limitations of unfractionated heparin Although highly effective in the prevention and treatment of venous thromboembolism, acute coronary syndromes, and in patients undergoing surgery utilizing cardiac bypass, heparin has well described limitations categorized as 'biophysical' and 'pharmacokinetic'.[6–8] The biophysical limitations reflect the inability of the H-AT complex to inactivate fXa bound to platelets within prothrombinase, the phospholipid-membrane bound factor Va (fVa)-fXa complex, in addition to the resistance of fibrin-bound thrombin to inactivation by heparin.[8]

Pharmacokinetic limitations are caused by the binding of heparin to plasma proteins including platelet factor 4 (PF4), fibrinogen, factor VIII and histidine-rich glycoprotein.[6 9 10] As many heparin-binding proteins are acute-phase reactants, the phenomenon of heparin resistance is often encountered in acutely ill patients, in patients with malignancy, and during peri- or post-partum periods.[11] In addition to altered mechanisms of heparin clearance, heparin resistance has also been associated with drug-induced causes including aprotinin[12] and nitroglycerin,[13] although the latter is controversial. Its association with low antithrombin levels is also a point of heated discussion in the literature; heparin therapy produces a decrease in circulating antithrombin that is independent of the initial dose, is detectable after 1 day, and peaks after 2–4 days. Cessation of therapy leads to a normalization of levels,[14 15] but it is not clear if this reduction in AT contributes to the heparin resistance seen in patients undergoing treatment for venous thromboembolism, or in patients undergoing cardiac bypass surgery.

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The complexities involved in accurately assessing the anticoagulant effect of heparin in the laboratory do not simplify matters. The APTT is the most commonly used laboratory test for monitoring heparin in the UK.[15] As a global test of the intrinsic and common pathways, the APTT is influenced by blood collection techniques including: sampling tube composition; type of anticoagulant used; and timing of sample collection in relation to therapy,[15] to avoid PF4-mediated neutralization of heparin.[9] APTT reagents have different levels of heparin responsiveness producing a further problem.[15] There are a number of situations in which the APTT lies within the target range for heparin therapy whilst the heparin level is suboptimal, such as the presence of acquired and congenital clotting factor deficiencies, the presence of lupus anticoagulant, and the effect of warfarin. In contrast, the previously described conditions causing heparin resistance lead to situations where excessive doses of heparin are required to prolong the APTT into a therapeutic range. In a randomized controlled trial by Levine, 131 patients with heparin resistance were studied, and the effect of monitoring the APTT was compared to anti-Xa heparin activity. No significant difference was noted in terms of clinical outcome, but the group monitored by anti-Xa levels required significantly less heparin.[16] The development of heparin resistance is therefore a clear indication for the use of the heparin assay to measure the anticoagulant effect of this drug.

Modern heparin assays are based on chromogenic anti-fXa assays which measure the heparin-antithrombin inhibitory effect towards fXa. Like all biological assays, there are limitations; and results may differ depending on the technique employed and on the presence or absence of exogenous antithrombin in the sample. Although originally time-consuming, a new bedside anti-fXa monitoring test has recently been developed which permits a quicker and more accurate assessment of the true anticoagulant effect of heparin, and which may prove invaluable in the context of cardiac bypass surgery.[17] At present, the ACT is the most commonly used laboratory test to control heparin effect on extracorporeal membranes. However, ACT results are highly dependent on the instrumentation employed, and may also vary with the presence of haemodilution and hypothermia.[18]

Cardiac surgery produces a unique activation of coagulation due to the presence of the cardiopulmonary bypass (CPB) circuit.[19] Whilst not yet fully elucidated, the mechanisms of activation of coagulation during CPB may involve activation of fX by the tissue factor-mediated pathway within the pericardial cavity, in addition to direct generation of fXa on the surface of monocytes by Cathepsin G, a substance released from activated monocytes.[20] The inhibition of fXa in these situations involves the AT-dependent mechanism of action of heparin. The imbalance caused by the increased activation of fX *via* the extrinsic pathway relative to the generation of fXa by the intrinsic pathway may, in part, account for the reduced effect of heparin in some patients during CPB. Currently it is believed that haemostasis is maintained by the generation of fXa by the X-ase complex. The activity of this membrane complex is directly inhibited by heparin[5] and may contribute to the anticoagulant effect of heparin in situations where intrinsic activation of fX plays a major role. In its turn, this suggests that the relative contribution of the intrinsic and extrinsic pathways towards fXa generation may be linked to the dosage of heparin required to achieve a desired anticoagulant effect. In general, heparin is administered at a dose of 3 mg kg^{-1} body weight to prevent extracorporeal clot formation, with repeated doses to maintain the ACT greater than 400 s. This heparin regime was, however, established empirically and aims to maintain levels at 3 IU ml^{-1},[19] so is this level of heparinization necessary?

Are there any potential solutions to the problems created by heparin resistance during CPB in the foreseeable future? Considering alternative therapies, argatroban, a selective, reversible thrombin inhibitor, has been successfully used as an anticoagulant in canine models of CPB in combination with heparinized CPB circuits.[21] Another direct thrombin inhibitor, hirudin, originally derived from the salivary glands of the medicinal leech, *Hirudo medicinalis*, and now available in recombinant form, has been successfully used to prevent clotting within the CPB circuit in patients with heparin-induced thrombocytopenia. There are drawbacks; the antithrombotic effects still require monitoring by a whole blood assay based on the prothrombin-activating snake venom, ecarin, known as the ecarin clotting time,[22] and reversibility of the drugs depends on haemodialysis. The role of these direct thrombin inhibitors, in addition to other new anti-fXa inhibitors such as inhibitors of the tissue factor pathway and Pentasaccharide (Org31540/SR90107A), and heparin-coated CPB circuits, have yet to be evaluated in terms of safety and efficacy by appropriately powered, prospective studies.[23]

Perhaps the most promising of these drugs may be pentasaccharide, the first of a new class of highly selective fXa inhibitors. Given as a once daily subcutaneous dose, it has a pharmacokinetic profile such that the monitoring is not required. Phase II and III trials have demonstrated high efficacy compared to low molecular weight heparins in the prevention of venous thromboembolism, and preliminary results in cardiology trials have also shown great promise.[24]

At present, heparin remains the optimal means of anticoagulation in CPB circuits, but improvements are needed in terms of practical bedside monitoring of its anticoagulant effect which, in turn, may permit a reassessment of the optimal level of ACT to achieve prior to starting the bypass circuit.

There is still much to learn about heparin resistance. In the context of venous thromboembolism, is heparin resistance of any clinical relevance? What is the outcome in patients treated with empirical doses of heparin when the APTT cannot be prolonged into the therapeutic range? In the context of cardiac bypass surgery, where activation of coagulation and fibrinolysis involve as yet poorly understood mechanisms, and where postoperative bleeding complications lead to increased blood product usage and other postoperative complications, what is the optimal means of monitoring the anticoagulant and antithrombotic effect? With the recent development of delivery systems that make it possible to give heparin orally,[25] and the development of new synthetic indirect and direct fXa inhibitors, these questions become increasingly pressing.

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Editorial II

Haemodilution enhances coagulation

The effect of haemodilution on enhancing coagulation is well described. In this issue, Ng, Lam and Chan[1] have avoided all the confounding variables of the stress response induced by surgery, and have identified enhanced coagulation to be a result of the haemodilution itself. This was achieved by comparing the onset of coagulation in two groups undergoing anaesthesia for hepatobiliary surgery: one group received fluid after starting anaesthesia; the other, acting as the control group, received no intravenous fluid after starting anaesthesia. The two groups were compared, using Thrombelastograph® and routine tests, before commencing any surgical stimulus. In doing so, the enhancement of clot formation after haemodilution has been reconfirmed.

In analysing the effect of enhanced coagulation occurring with haemodilution, the entire clotting cascade has been explored in order to define exactly at which point, and through which mechanism, this occurs. There may well be many factors that have an impact on the fine balance of coagulation enhancement and inhibition. A lowering of haematocrit has been described as decreasing coagulation, on the basis of decreased blood viscosity leading to a faster arterial blood flow,[2] but these authors did not comment on the microvascular circulation. On the other hand, the enhancement of clot formation, both *in vitro* and *in vivo*, following haemodilution with 0.9% saline and other crystalloid solutions, has been addressed by several authors.[3–9] Furthermore, coagulation following haemodilution is not mediated via platelet–endothelial interaction, as it still persists after platelet function has been removed through the administration of aspirin.[10] The effect is significant because it casts doubt on previous studies on coagulation effects caused by various colloids while using crystalloids as a control. With this complicated and interactive dynamic system, it is also difficult to measure only end-points and obtain an accurate result. On the other hand, the Thromboelastograph® (TEG) measures the coagulation process in whole blood, rather than testing the activity of coagulant factors in anticoagulated plasma, as is commonly done in conventional analysis of coagulation. Thrombelastography is a technique first developed by Hartert in 1948.[11] It was subsequently developed further in various areas.

The enhancement of coagulation following crystalloid haemodilution was first described in the 1950s by Monkhouse[12] and Tocantins.[13] In 1975, Vinnazzer and colleagues[14] found a postoperative hypercoagulable state in the control (saline) group, and an insignificant change in the test (hydroxyethyl starch) group of their investigation. However, it is difficult to determine if the enhanced coagulation was the result of the saline therapy, or surgery; similarly, the apparently normal coagulation profile in the starch group could be interpreted either as a negligible effect of the starch on coagulation, or as an impairment of surgery-induced enhanced coagulation. In another study, Popov-Cenic and colleagues[15] referred to the effect of surgery on enhancing coagulation and the modification thereof by hydroxyethyl starch, but did not attribute the enhancement as being the result of haemodilution with crystalloid. The effect has been demonstrated *in vivo* in normal volunteers, in whom rapid administration of crystalloid resulted in the onset of enhanced coagulation, with the effect being absent in the colloid (hydroxyethyl starch) group.[4] Janvrin,[16] in 1980, not only described the enhancement of coagulation, but also demonstrated an increased risk of deep vein thrombosis in a group of patients receiving perioperative intravenous fluid, compared with a control group receiving no intravenous infusion.

When a blood vessel is damaged, it is essential that the final products of the haemostatic system are restricted to the site of damage. At the same time, an adequate flow needs to be maintained through the vascular system in order to have sufficient organ perfusion. The entire clotting process, from its initiation through to fibrin production, must therefore be spatially restricted in the vasculature to prevent an unrestricted coagulopathy. Coagulation is an intricate system, with multiple interactions between factors, including the coagulation and fibrinolytic proteins, platelets, activators and inhibitors. The extrinsic and intrinsic pathways do not function independently, but rather sequentially. Initial thrombin production via the faster extrinsic pathway is amplified by the slower intrinsic pathway. This occurs through both the direct activation of factor IX by factor VIIa/tissue factor complex, and via the positive thrombin feedback into the intrinsic pathway. Thus, haemostasis involves a highly complex interaction between clot formation and clot lysis to avoid uncontrolled action in either direction. This is accomplished by numerous positive and negative inhibiting and activating feedback mechanisms.

It must be emphasized that thrombin generation is the central biochemical reaction in both normal haemostasis and thrombosis.[17] The production of thrombin is self-reinforcing because of its feedback activation of numerous coagulation proteins (factors V, VIII, XI and VII) that contribute to thrombin production. Positive feedback in coagulation plays a major role in the architecture of the system.[18] While thrombin is also involved in other pathways such as platelet aggregation and in the stimulation of the fibrinolytic pathway,[19] its positive feedback into the intrinsic pathway is the most important factor. The cause for the enhanced coagulation occurring after haemodilution may well be attributed to a decrease in the concentration of the coagulation inhibitors, lowering the threshold for positive feedback to occur into the coagulation pathway. Nossel and co-workers have demonstrated that activated fibrinopeptides are continuously being formed in plasma, and concluded that, *in vivo*, normal plasma contains background levels of activated thrombin.[20 21] On the other hand, Jesty and colleagues found that inhibition of the positive-feedback loop, through the effect of anticoagulants, plays a role in modulating the exponential enhancement of the coagulation cascades.[22] This in turn confers threshold properties on the system: if the level of activated thrombin is below the threshold, no response occurs, whereas if the level rises above the threshold, the response should be at, or near, maximum. As a result, once the thrombin level has overcome the anticoagulant-induced threshold, there is an exponential increase of further thrombin formation, thus ensuring that a clot is formed. The ability of the entire system to cope with background non-zero levels of activated clotting enzymes, without generating a response, implies that the balance of intravascular coagulation is protected against sub-threshold stimuli. The second-order kinetics of the action of anti-thrombin III (AT III) mean that the rates of inhibition of its target enzymes are a function of its concentration.[22–24] Clinical evidence has shown that a decrease in concentration of AT III, to below 70% of normal is linked to an increased risk of thrombosis, particularly venous thrombosis. Since at this level there is still a massive excess of AT III relative to activated thrombin, partial inhibitor deficiency is likely to be a kinetic rather than a capacity defect. The role of inhibitors (AT III, proteins C and S, and tissue factor inhibitor *inter alia*) is therefore important in control and cessation of this cascade, thereby preventing dissemination of intravascular thrombosis. Moreover, the actual *quantity* or *level* of an individual factor does not necessarily reflect its functional status.[16] It is interesting to note that in their findings, Ng and colleagues[1] describe a dilution-related percentage decrease in all the measured factors. This included AT III and fibrin, which showed a trend towards a greater decrease from time zero than did haemoglobin. However, the thrombin–anti-thrombin (TAT) levels remained at a predilutional value in the dilution group, even showing an increase at 30 min. This occurred in spite of the haemodilution, while in the control group a decrease in TAT values occurred after initiation of anaesthesia. One may speculate that this represents an increase in the generation of activated thrombin following haemodilution, which was deactivated by the AT III, thus increasing the level of TAT. Because the activated thrombin makes up a minute fraction of the total prothrombin and anti-thrombin concentrations, and there is a one-to-one enzyme-to-inhibitor reaction of thrombin with AT III,[25] even a doubling of the activated-thrombin levels will not necessarily result in a significant decrease in the absolute level of AT III.

Conversely, when partially maintaining the coagulation threshold after dilution has occurred by keeping the concentration of AT III within the normal range in the diluent, the effect of enhanced coagulability resulting from dilution can be attenuated but not completely inhibited.[17] Since AT III is only one of several positive-feedback inhibitors acting on the coagulation cascade[24] (accounting for only 40–50% of the effect), it is possible that one could produce greater attenuation of the dilution-enhanced coagulation by keeping the levels of the other naturally occurring inhibitors of coagulation constant.

Does this have a clinical effect? Given the findings of an enhancement of coagulation following haemodilution, one can speculate that when an individual has a significant loss of blood, with rapid restoration of circulating blood volume from the interstitium, the onset of coagulation may be enhanced. It is interesting to observe that there may have been a survival benefit for the evolution of such a mechanism – when internal haemodilution occurs after blood loss, enhanced coagulability may prevent further haemorrhage in the wild state. However, a point may be reached where bleeding occurs as the clotting factors are used up through enhanced clot formation at a capillary level. This in turn leads to a marked increase in bleeding, as an imbalance between procoagulant factor activation and anticoagulants, or enhanced fibrinolysis, occurs – the syndrome of disseminated intravascular coagulopathy (DIC). In the natural state, this may well result in the death of the individual. Indeed, decreased plasma concentration of AT III may be indicative of the role of DIC in the pathogenesis of multiple organ dysfunction syndrome,[26] its baseline value correlating with mortality, and its plasma concentration being decreased in DIC, particularly in sepsis and shock.

This poses the question of whether any individual at risk of DIC could be prevented from sparking off their original enhancement of coagulation, before the entire chain reaction of DIC is started, and whether this may be achieved by preventing too rapid a fluid replacement, thereby preventing rapid dilution. In a less overwhelming reaction, the formation of deep vein thromboses and pulmonary emboli could be prevented by decreasing or avoiding haemodilution.[16]

In a recent study (unpublished observation) examining the effect of blood loss and autodilution, it appeared that a slow autodilution of blood to replace a 10% loss does not show the imbalance between anticoagulants and spontaneously activated coagulants that occurs after a *rapid* large-volume (20–30%) haemodilution. It is of interest to note that a 10% loss of blood volume in a healthy person is easily compensated for by the sympathetic response, through an increase in blood-vessel tone. This maintains end-organ perfusion and results in a slow re-expansion of blood volume, as is evidenced by the fact that donation of a unit of blood, which makes up 10% of circulating blood volume, does not impair the donor's normal daily function, nor render them hypercoagulable.

How does one put all of this together? Suffice it to say that Ng and colleagues[1] have again demonstrated the effect of enhanced coagulation following haemodilution. Their work is done in a controlled *in vivo* setting, which confirms the findings without the effect of any confounding variables. While it is still difficult to prove a clinical difference in outcome between diluted and undiluted groups, these findings, when seen in the context of previous work, suggest that for minor surgery in healthy individuals, intravascular fluid infusions should be avoided, or, if rapid infusion is necessary, a low-molecular-weight starch should be considered.[4] Patients will compensate for their blood loss without haemodilution, and so will not be exposed to the potential risk of enhanced coagulation associated with rapid haemodilution. As Janvrin[16] indicated, perioperative administration of intravenous fluid is potentially harmful, and is not necessarily needed. In practical terms, having venous access does not imply the need to have an infusion running.

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Editorial III

'Ventilating in recovery'—the way forward: intensive therapy or postoperative critical care?

All anaesthetists in the UK are familiar with the concept of 'ventilating a patient in recovery.' In effect, this is the provision of critical care in the recovery ward, usually because of insufficient critical care resources. It is a largely unsatisfactory situation, but there is a paucity of data on the extent of the practice and the consequences for patients, and for their medical and nursing carers. In this issue, Ziser and co-authors quantify the problem in their hospital in Haifa, Israel, and review some of its challenges.[1] Their solution is to bring the data to the hospital management with a request for more ITU beds. This is a counsel of perfection, which will find more or less sympathy from the management of different UK trusts. Is it possible to make a virtue of necessity, and provide postoperative critical care in a satisfactory operating theatre environment?

The Israeli experience is well recognized by British anaesthetists. Four hundred patients were admitted to their Post-Anaesthesia Care Unit (PACU) in 2.5 yr because they required a critical care or ward bed, which was not available elsewhere in the hospital. They are described as 'overflow' patients. Ten per cent of these patients stayed longer than 24 h. The mean stay was over 12 h. Over 70% of the patients were mechanically ventilated and had invasive monitoring.

First, it is necessary to demonstrate why *ad hoc* management of these cases in the recovery ward is a bad thing. After all, intensive therapy is an expensive resource (£1200–1500 per bed per day in the UK); if adequate care can be given elsewhere at times of bed saturation, surely this may be more cost effective? Ziser and co-authors identify the following adverse factors associated with use of the recovery area:

- The greatest patient load occurred at night, coinciding with lowest staffing levels.
- Problems with relatives visiting patients.
- The effect on routine postoperative patients of observing dying patients.
- Continuity of surgical cover.

Similar problems have been experienced since 1990 at the Royal Liverpool University Hospitals. A long-standing under-provision of intensive care beds led to large numbers of inter-hospital transfers of critically ill patients, and an expanding number of patients cared for in an inadequately staffed and poorly equipped recovery room. As a result of an audit carried out in 1995, a successful approach was made to purchasers for additional funding, both to increase the number of intensive care beds by two, and resource the recovery overflow work. However, this did little to reduce the pressure on the recovery ward. In spite of improved equipment and staffing levels, staff morale fell There was a feeling that the critically ill patients were receiving a second-class service Recovery nurses felt they were inexperienced and under-trained to care for ITU patients. It was difficult within the on-call system to provide anaesthetic and intensivist continuity of care. The routine work of the recovery ward was at times severely disrupted by the critical care 'bays'. At the same time, high occupancy of intensive care facilities in the hospital and region made stopping the service impossible.

Despite full ITU occupancy and utilization of the recovery ward, postponement of major surgery because of a lack of a postoperative critical care bed was frequent (two to three patients per week), and sufficient to jeopardize the achievement of Trust targets. Patients were receiving suboptimal care (although the best in the circumstances), routine major surgery was being disrupted, and staff morale was low, causing problems with recruitment and retention.

Two options were considered. First, the approach, as advocated by Ziser and co-authors,[1] to greatly increase intensive therapy provisions; or, secondly, to provide a postoperative critical care facility in the operating theatres.

The ITU capacity was increased from 12 to 13 beds. Further expansion, however, would have been very difficult. A new building would have been required, new staff would need to be recruited, and medical rotas would need to be redesigned so that patients could be safely cared for Consequently, this development would have required considerable investment from outside funding bodies.

Although a plan is in place to expand the hospital's high dependency capacity, this would not address the patient who required ventilatory support, which accounted for a large proportion of the elective surgery postponements. There is very little published about alternative models of care apart from intensive therapy and high dependency. Prien and von Aken[2] suggest that the PACU could be used to improve the condition of a postoperative patient, allowing eventual discharge to an area of lower dependency immediately after surgery. This was the model we adopted

Space for a four bedded critical care unit had been identified in a redundant part of the forward waiting area in the operating theatres. This area could be rebuilt for a relatively small capital investment. The main problem was to address medical and nursing staffing cover in order to provide good quality care. However, it was possible to do this within Trust resources. Consequently, the decision was taken to make detailed plans for the development of a Post Operative Critical Care Unit (POCCU) on the grounds that this was readily achievable, whereas further ITU expansion would remain a longer-term aspiration. Consequently, a successful bid was made for central investment from funds for critical care development, and the POCCU opened on

Table 1 Admissions to the Royal Liverpool University Hospitals POCCU for 7 months in 2001

2001	February	March	April	May	June	July	August
Admissions (*n*)	45	35	32	45	41	37	39
Bed occupancy (%)	84	58	80	63	75	57	58
Postoperative patients (*n*)	40	34	27	30	32	28	25

December 1, 2000. Does experience so far justify this approach?

Table 1 shows that on average approximately 40 patients per month were cared for in the POCCU. Of these, 78% were admitted from the operating theatre after elective or emergency surgery. Although the POCCU did admit patients who were 'ITU spill over', early fears that the unit would be swamped by patients needing ITU, who had no bed available, were not borne out.

Several factors affected these figures. It has been a strict policy not to accept referrals to the POCCU from outside the Trust, as the POCCU is not an intensive therapy unit. However, more importantly, the POCCU has allowed greater flexibility of critical care bed use. For instance, less dependant patients may be transferred from the ITU to the POCCU, to make space for a more seriously ill patient. This has resulted in longer mean stays on the ITU (R. Wenstone, personal communication), but has reduced the number of periods when no critical care bed is available in the Trust. Consequently, cancellation of elective major surgery has been reduced from two to three per week, to an average of three per month. This ranges from a figure of no cancellations in 1 month to six cancellations in another.

The POCCU has been staffed by anaesthetists rather than intensivists. Initial fears that clinical skills would be inadequate have been allayed. However, as a result of the constraints of modern anaesthetic training, the extra level of cover has been from an extra consultant tier. During the period from hours 08:00 to 20:00, a consultant anaesthetist whose duty is to the emergency service including the POCCU is on site. After 20:00, the emergency service covers the POCCU as well as other non-elective work. If the number of hands is insufficient, a 'second on call' consultant is available. The initial informal visits and advice by intensivists has been formalized into the developing ITU outreach service. Thus, critically ill postoperative patients can be cared for without an increase in ITU establishment, and without compromising the quality of care.

The nursing staff of the POCCU are provided from recovery ward staff. Prior to the opening of the unit, several experienced ITU nurses were recruited. This has allowed recovery nurses with no critical care experience to be supported while training, and allows all nurses to rotate through the less stressful recovery ward environment. This has proved an attractive role with nursing applicants. Ongoing training includes regular attachments in the ITU, which has improved relations between the two groups of staff.

Aps[3] describes a similar solution in the care of postoperative cardiac surgery patients in the Guy's and Saint Thomas' Hospital. Using 'creative demolition', a five (later nine) bedded Overnight Intensive Recovery (OIR) was established adjacent to the recovery ward. From 1983 to 1999, 55% of cardiac surgery patients received their postoperative care in the OIR rather than the ITU, and the OIR is currently managing 65–75% of cardiac cases. Aps emphasizes the vital importance of any postoperative critical care facility being considered separately from ITU, although acknowledging that ITU support is essential. He estimates that the annual cost of a four bedded OIR is £94 500 per bed (compared with £380 000 for an intensive therapy bed), but points out that less ambitious projects will be cheaper.

Ziser and co-authors[1] have quantified a problem, which all anaesthetists have to deal with regularly, 'ventilating patients in recovery'. The Royal Liverpool and Guy's experience shows that the establishment of a critical care facility in the operating theatre may have advantages over ITU expansion.

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BJA

CLINICAL INVESTIGATIONS

In vivo effect of haemodilution with saline on coagulation: a randomized controlled trial[†‡]

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Background. Previous studies have shown that 10–30% haemodilution with crystalloid may induce a hypercoagulable state demonstrable by using the Thrombelastograph® (TEG). While most are *in vitro* studies, the few *in vivo* studies are limited by confounding surgical or 'environmental' factors. We conducted this randomized controlled study to evaluate the coagulation changes associated with *in vivo* haemodilution.

Methods. Twenty patients undergoing major hepatobiliary surgery were randomly allocated to one of two study groups. Group H (n=10) had 30% blood volume withdrawn over 30 min and replaced with saline. Group C (n=10) did not have any blood withdrawn. Blood samples were taken in both groups at 10, 20 and 30 min. Native TEG, complete blood count, coagulation profile, fibrinogen, antithrombin III, protein C and thrombin–antithrombin complex concentrations were measured.

Results. Compared with Group C, Group H patients had significantly greater shortening of r-time at 30 min (–30% *vs* +36%), greater shortening of k-time at all time points (–36% *vs* +17% at 10 min; –37% *vs* +44% at 20 min; –45% *vs* +49% at 30 min), and greater widening of α at 30 min (+71% *vs* +4%). The decrease in antithrombin III and other natural procoagulants and anticoagulants closely followed that of haematocrit, with the exception of thrombin–antithrombin complex.

Conclusion. *In vivo* haemodilution of up to 30% with saline can induce a hypercoagulable state. The mechanism remains unclear as disproportionate dilution of natural anticoagulants was not detected. Thrombin–antithrombin complex concentration remained stable despite haemodilution in Group H, which may suggest increased thrombin generation.

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Acute haemodilution of 20–30% with crystalloid has been shown to induce a hypercoagulable state demonstrable using the Thrombelastograph® (TEG). The characteristic changes include shortening of r-time and k-time, which indicates accelerated rate of clot formation, as well as widening of the angle (α), which indicates accelerated rate of clot stiffening Most studies demonstrating this effect were performed using *in vitro* haemodilution.[1–6] Only two studies have provided evidence that hypercoagulability induced by acute crystalloid haemodilution can also be demonstrated *in vivo*.[7 8] In one of these studies, we demonstrated that in patients undergoing major surgery, only those who had considerable blood loss and haemodilution will develop significant hypercoagulability as measured on TEG.[7] However, there are obvious limitations to attributing all the changes we observed in the previous

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study to haemodilution *per se*. For example, tissue damage is likely to be more extensive in operations involving greater blood loss, and this may induce a more significant hypercoagulability response. Others have demonstrated the development of hypercoagulability *in vivo* in healthy volunteers receiving only an intravenous infusion of 1 litre normal saline.[8] Their findings have strengthened the hypothesis of the development of a hypercoagulability state with mild haemodilution.

However, a recent study reported that a hypercoagulable state might also be induced in patients during preparation for regional anaesthesia *per se* without administration of any drugs or intravenous fluids.[9] This suggested that some of the changes observed in previous *in vivo* studies could be attributable to confounding factors such as patient anxiety or insertion of intravenous lines. We therefore conducted this randomized controlled study to investigate the effect of up to 30% acute crystalloid haemodilution on coagulation. The design of the study will enable us to eliminate the effect of any confounding factors. We also measured the changes in various procoagulant and anticoagulant markers to delineate the mechanism underlying any changes observed. This includes measuring changes in fibrinogen, antithrombin III (AT III) and protein C concentrations, to detect any disproportionate dilution between procoagulants and anticoagulants. We also measured the concentration of thrombin–antithrombin complex to detect any increase in thrombin generation.

Methods

With institutional Ethics Committee approval and written informed consent, we recruited into the study ASA I–III patients undergoing major elective hepatobiliary surgery. These patients were scheduled to have intraoperative collection of autologous blood and acute isovolaemic haemodilution. We excluded patients with known haemostatic disorders, patients taking medication known to interfere with haemostasis, including oral contraceptives, and patients with severe anaemia, or cardiovascular or respiratory disease.

Eligible patients were randomly allocated to one of two study groups: haemodilution group (Group H) and control group (Group C). In both groups, general anaesthesia was induced with fentanyl 1.5–2 μg kg^{-1}, thiopental 3–4 mg kg^{-1} and atracurium 0.5 mg kg^{-1}. The patient's trachea was intubated and the lungs ventilated with oxygen/air/isoflurane Immediately after induction of anaesthetic, a 14 or 16G peripheral cannula (Angiocath, Becton Dickinson, Mexico), a right internal jugular cannula (Angiocath, Becton Dickinson, Mexico) and an arterial cannula (Insyte, Becton Dickinson, USA) were inserted. Autologous blood collection was performed via the internal jugular line, normal saline replacement via the peripheral venous line, and blood sampling via the arterial line.

The study period was divided into three 10-min intervals. Within each 10-min interval, in group H patients 7 ml kg^{-1} of blood was removed and simultaneously replaced with 14 ml kg^{-1} normal saline; Group C patients were undisturbed. The volume of saline infused was chosen to maintain normovolaemia according to the nomograms developed by Drobin and colleagues.[10] In both groups, blood samples for TEG and other measurements were taken at the end of each 10-min interval. At the end of the three 10-min intervals, Group H patients had had approximately 30% of their blood volume removed and replaced with normal saline. Three sets of blood samples for analysis were collected from each patient. If blood removal was completed within 10 min in a Group H patient, the patient remained undisturbed until the end of the 10-min interval, when blood samples were taken.

Blood samples were taken using a double syringe technique; the first 10 ml collected was discarded. Each sample was then sent for the following analysis: (i) immediately for haemoglobin (Hb) on a haemoglobin photometer (Hemocue, Hemocue AB, Angelholm Sweden), (ii) within 3 min for measurement by TEG (Haemoscope Corporation, Skokie, IL, USA) as fresh whole blood without celite. TEG parameters recorded included r-time, k-time, maximum amplitude (MA) and α. (iii) Stored in 0.109M trisodium citrate tubes (Vacuette, Greiner Labortechnik, Germany), 9 parts to 1 by volume for prothrombin time (PT), INR, activated partial thromboplastin time (aPTT), fibrinogen, protein C, AT III and thrombin-antithrombin complex. (iv) Stored in EDTA tubes (Vacuette, Greiner Labortechnik, Germany) for Hb, platelet count (PLT) and white cell count (WCC).

Complete blood counts were performed on an automated cell counter (Gen-S, Beckman-Coulter, USA). PT and aPTT were measured immediately after collection of blood samples and centrifugation at 3000 r.p.m for 10 min on an automated coagulometer (MDA-180, Organon-Technika, USA). Fibrinogen level was assayed by the Clauss method using a semi-automated coagulometer (Cobas Fibro, Roche, Switzerland). Tests for other coagulation parameters were batch processed, and plasma samples were stored at −70°C. Assays for protein C and AT III were done by chromogenic assays according to the manufacturer's instructions using commercial kits (Stachrom protein C and Stachrom AT III, both from Diagnostic Stago, France) on an automated coagulometer (ACL 3000™, Instrumentation Laboratory, Italy). Thrombin–antithrombin assay was performed by sandwich enzyme immunoassay using a commercial kit (Enzygnost TAT, Behring, Germany) according to the manufacturer's instructions.

Surgery was started after completion of blood sampling. More normal saline was then administered in Group H patients to keep the central venous pressure above 5 mm Hg, and autologous blood collection was performed in Group C patients.

Table 1 Patient characteristics Data are mean (SD) or actual numbers

	Group H (*n*=10)	**Group C** (*n*=10)
Age (yr)	58.0 (43–70)	49.0 (19–65)
Body mass index (kg m^{-2})	20.6 (3.99)	21.8 (3.74)
Sex ratio (M/F)	5/5	8/2
Smoking (Y/N)	1/9	2/8
Diagnosis		
Hepatocellular carcinoma	7	7
Cholangiocarcinoma	1	1
Retroperitoneal tumour	–	1
Metastatic liver tumour	1	–
Carcinoma of pancreas	–	1
Carcinoma of gallbladder	1	–

Statistics

Statistical analysis was performed using the software programme Statistica release 4.5 (StatSoft, Tulsa, OK, USA). Intergroup comparisons of the changes in TEG parameters from control at each time point were performed using the Mann–Whitney *U* test. Intergroup comparisons of other coagulation tests and factors were performed using the unpaired two-tailed Student's *t* test. Changes in TEG parameters and coagulation tests over time were compared with the preoperative value in each group by repeated measures ANOVA. Where a statistically significant difference was detected, further paired comparisons were made between individual time points and the preoperative values using the Tukey HSD test. The significance level was set at $P<0.05$.

The sample size of ten in each group allowed us to detect with 80% power at this significance level a 30% difference in any parameter, assuming the standard deviation of the parameters to be approximately 25%. These approximations were estimated from previous similar studies.[4 8]

Results

A total of 20 patients were recruited. There were ten patients in each group. Patient characteristics and surgical details are given in Table 1.

Changes in r-time, k-time, MA and α are summarized in Figures 1–3. Group H had a significantly shorter r-time at 30 min (–30% *vs* +36% in control group C, $P<0.05$), a shorter k-time at 10, 20 and 30 min (–36% [Group H] *vs* +17% [GroupC], $P<0.01$; –37% *vs* +44%, $P<0.05$; and –45% *vs* +49%, $P<0.05$, respectively) and a wider α at 30 min (+71% *vs* +4%, $P<0.05$).

Changes in WCC, PLT, INR, aPTT, fibrinogen, thrombin–antithrombin complex, AT III and protein C are summarized in Table 2. Group H patients had a longer aPTT at 20 min (36.0 s [Group H] *vs* 31.3 s [Group C], $P<0.05$), lower fibrinogen at 30 min (2.1 g $litre^{-1}$ *vs* 3.1 g $litre^{-1}$, $P<0.05$) and lower AT III at 30 min (0.64 IU ml^{-1} *vs* 0.90 IU ml^{-1}, $P<0.05$). There were no statistically significant

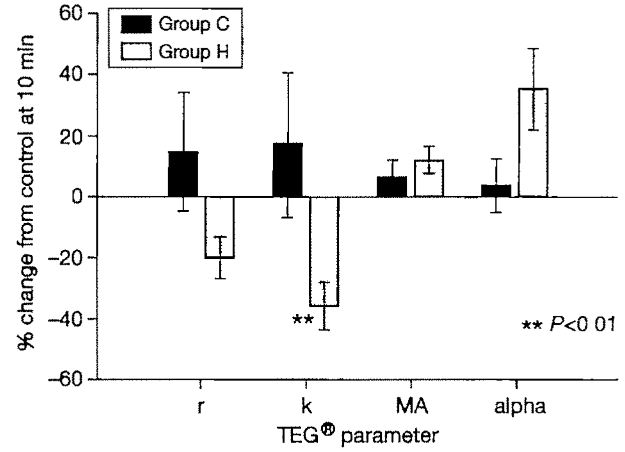

Fig 1 Comparison of TEG parameters (r-time, k-time, MA, α) between Group H and Group C at 10 min $^{**}P<0.01$ Group H *vs* Group C

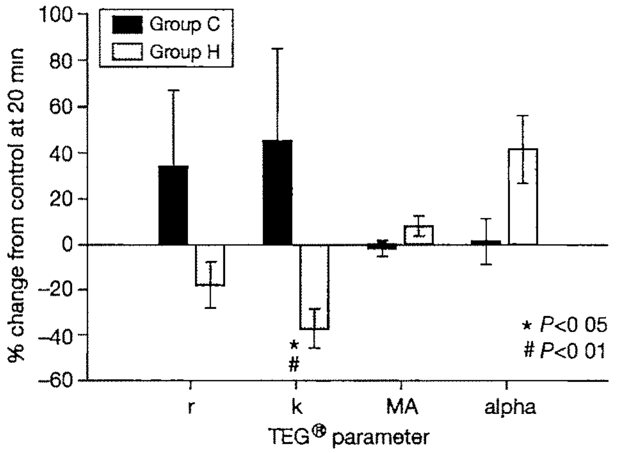

Fig 2 Comparison of TEG parameters (r-time, k-time, MA, α) between Group H and Group C at 20 min * $P<0.05$ Group H *vs* Group C, $^{\#}P<0.01$ compared with time zero

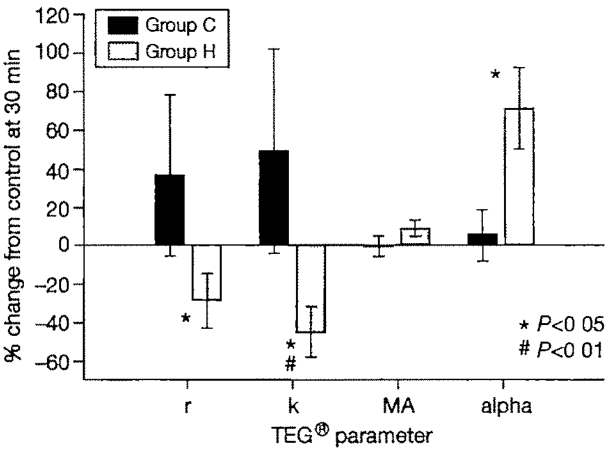

Fig 3 Comparison of TEG parameters (r-time, k-time, MA, α) between Group H and Group C at 30 min * $P<0.05$ Group H *vs* Group C, $^{\#}P<0.01$ compared with time zero

Table 2 Change of cellular and haemostatic parameters over time Group H *vs* Group C Data are mean (SD). *$P<0.05$ Group H *vs* Group C (Student's *t*-test); †$P<0.01$; ‡$P<0.001$ compared with time zero (repeated measure ANOVA followed by the Tukey HSD test); PLT, platelet count, APTT, activated partial thromboplastin time; FIB, fibrinogen, AT III, antithrombin III, TAT, thrombin–antithrombin complex, PC, protein C, WCC, white cell count

		0 min	**10 min**	**20 min**	**30 min**
Group H (*n*=10)	PLT ($\times 10^9$ litre^{-1})	202 (75)	186 (71)	171 (61)‡	158 (59)‡
	INR	1.04 (0.12)	1.10 (0.098)	1.24 (0.288)	1.29 (0.080)
	APTT (s)	34.9 (4.5)	37.9 (6.6)	36.0 (2.8)*	42.2 (9.6)
	Fibrinogen (g litre^{-1})	3.18 (0.97)	2.70 (0.92)†	2.33 (0.79)‡	2.14 (0.67)*‡
	AT III (IU ml^{-1})	0.92 (0.26)	0.80 (0.23)‡	0.71 (0.22)‡	0.64 (0.20)*‡
	TAT (μg litre^{-1})	10.64 (6.88)	11.87 (8.10)	9.20 (3.81)	12.75 (7.41)
	PC (IU ml^{-1})	0.91 (0.24)	0.83 (0.24)	0.74 (0.23)‡	0.69 (0.19)‡
	WCC ($\times 10^9$ litre^{-1})	6.07 (2.39)	5.69 (2.48)	5.19 (2.13)‡	4.75 (1.90)‡
Group C (*n*=10)	PLT ($\times 10^9$ litre^{-1})	199 (78)	205 (81)	206 (81)	198 (72)
	INR	1.04 (0.06)	1.07 (0.07)	1.08 (0.07)	1.08 (0.08)
	APTT (s)	31.5 (4.0)	34.2 (8.6)	31.3 (4.8)*	36.5 (11.9)
	FIB (g litre^{-1})	3.29 (1.42)	3.17 (1.30)	3.17 (1.40)	3.07 (1.16)*
	AT III (IU ml^{-1})	0.96 (0.22)	0.90 (0.23)	0.89 (0.23)	0.90 (0.23)*
	TAT (μg litre^{-1})	22.03 (35.74)	26.69 (46.70)	12.44 (14.29)	15.09 (16.97)
	PC (IU ml^{-1})	0.85 (0.17)	0.82 (0.16)	0.80 (0.15) †	0.79(0.16)‡
	WCC ($\times 10^9$ litre^{-1})	6.67 (3.12)	6.43 (2.52)	6.60 (3.04)	6.40 (2.58)

differences in WCC, platelet count, INR, thrombin–antithrombin complex or protein C between Group H and Group C at any time point.

The changes in Hb over time in Group H and Group C are shown in Figure 4. There is steady haemodilution in Group H, with Hb values at 10, 20 and 30 min approximately 0.9, 0.8 and 0.7 times the Hb value at 0 min. Apart from thrombin–antithrombin complex, which became slightly elevated over time in group H (Table 2), all variables, including platelet count, WBC, fibrinogen, AT III and protein C, in Group H patients closely followed the decrease in Hb as a result of haemodilution (Fig. 5). There was a slightly larger drop in fibrinogen and AT III compared with Hb, but the difference was only significant statistically for fibrinogen at 10 min ($P<0.05$).

Discussion

Our present study has confirmed the development of a hypercoagulability state with mild saline haemodilution *in vivo*. The effect is demonstrable using TEG as a shortened r-time and k-time and widened α at levels of haemodilution of 20–30%. These TEG changes were not found in the control group. We can therefore eliminate 'environmental factors' as the cause of these changes.

The degree of haemodilution in our study is more profound than in a previous similar study.[8] While we detected most of our TEG changes at 20% or more haemodilution, the previous study reported changes at only 10% haemodilution. It is therefore difficult to compare the magnitude of changes of the various TEG parameters in the two studies. However, the pattern of the changes observed is highly consistent in both studies. The most significant changes are observed in k-time and α, followed by changes in r-time and a modest change in MA. The effect of saline haemodilution on coagulation seems to be most significant in accelerating the rate of growth of clot strength.

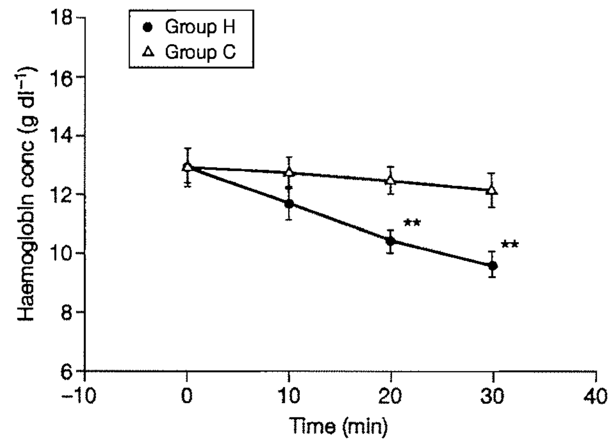

Fig 4 Change in haemoglobin concentration over time (**$P<0.01$ compared with time zero).

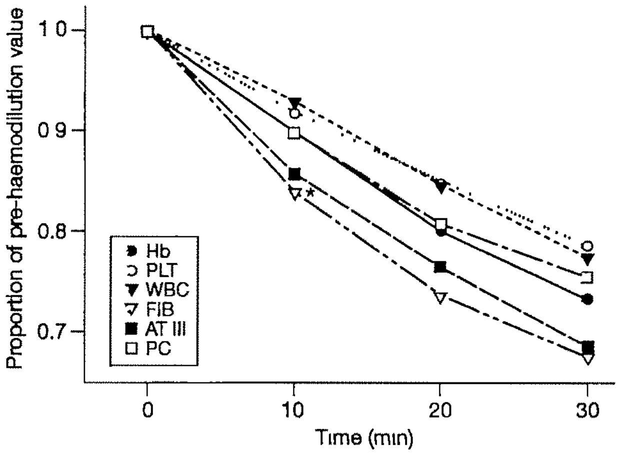

Fig 5 Proportional fall in various coagulation markers with respect to haemoglobin concentration in Group H (*$P<0.05$).

Our study failed to identify the exact mechanism by which these changes occurred. A disproportionate reduction in concentrations of natural anticoagulants such as AT III with haemodilution has previously been suggested as a possible explanation.[8] We are unable to demonstrate this in our present study. The decrease in AT III and protein C followed closely that of Hb as haemodilution progressed and was paralleled by similar changes in fibrinogen concentration. Although in terms of absolute concentration no disproportionate dilution of AT III or protein C was observed, reduction in the concentration of anticoagulants could still be responsible for the hypercoagulability we and others have reported. In particular, the impact of AT III on the natural balance between coagulation and anticoagulation may be much higher than that suggested by its absolute concentration. AT III is the most potent thrombin inhibitor.[11 12] As thrombin plays a key role in several positive-feedback loops in the clotting mechanism, small changes in the concentration of AT III may have a profound effect on the initiation and amplification of the clotting process.[13]

Unlike other factors, the concentration of thrombin–antithrombin complex remained unchanged despite haemodilution in Group H. On the other hand, concentrations decreased with time in Group C (Table 2). This implies an increase in thrombin generation rate in Group H particularly as the concentration of AT III was progressively decreasing with haemodilution.

We have confirmed that acute haemodilution of 20–30% with normal saline *in vivo* induces a hypercoagulable state as measured by TEG in surgical patients under general anaesthesia. Our results confirm the findings of previous *in vivo* and *in vitro* studies. However, it is important to note that changes in haemostatic function will be very different with more profound haemodilution,[14–16] or haemodilution with other colloid solutions.[1 2 6 14 17–20] For example, administration of hydroxyethyl starch for haemodilution will impair platelet function through its effect on von Willebrand factor.[21 22]

The mechanism by which hypercoagulability occurs with mild haemodilution with saline remains intriguing. However, we have demonstrated the possibility of increased thrombin generation as a cause for this phenomenon, thrombin–antithrombin complex concentrations remaining unchanged despite haemodilution. Other mechanisms which have not been investigated in our study could also be responsible for this interesting phenomenon. For instance, thrombus formation on a collagen-reinforced thrombogenic device has been shown to be inversely correlated to haematocrit,[23] and platelet adhesion to an artificial perfusion chamber was found to correlate inversely with blood viscosity.[24] The conditions of these studies are very similar to those during TEG measurement, namely activation of platelets and coagulation while blood is in contact with a foreign surface. The pattern of TEG changes observed in our study and that of a similar previous study[8] with predominantly shortening of k-time and widening of α also suggest that facilitation of platelet interaction with platelet activating surfaces during haemodilution may be a possible mechanism. Further studies are required to define more clearly the mechanism and the significance of hypercoagulability induced by saline haemodilution. Although haemodilution has been advocated as the treatment of choice for preventing various thromboembolic diseases such as stroke, the results of this treatment modality have not been conclusive.[25] In a large prospective cohort study, a U-shaped relationship was found between haematocrit and the risk of stroke, with the risk of stroke increased in patients with higher or lower haematocrit levels.[26] The relationship between haemodilution and thrombosis and haemostasis is probably more complicated and heterogenous than we used to believe. For practical purposes, the development of hypercoagulability and its potential risks must be considered whenever crystalloid haemodilution to 10–30% is employed clinically.

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Can a clinically useful aortic pressure wave be derived from a radial pressure wave?[†]

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Background. The information contained in arterial pressure waveforms is probably underused by most clinicians who manage critically ill patients. It is not generally known that an aortic pressure wave can be synthesized by applying a generalized transfer function to the radial arterial pressure wave. We validated a commercially available system, SphygmoCor™ (PWV Medical, Sydney).

Methods. Ascending aortic pressure waves were synthesized and comparisons were made between the synthesized aortic waveforms, the measured aortic and radial arterial waveforms. Ascending aortic pressure waves (catheter-tip manometer) and radial artery pressure waves (short fluid-filled catheter) were recorded simultaneously in 12 patients with angina pectoris (age 62–76 years) undergoing cardiac catheterization. Patients were studied at rest, following midazolam, sublingual nitroglycerin and during Valsalva manoeuvres.

Results. Both midazolam and nitroglycerin lowered mean arterial pressure but nitroglycerin caused a more selective decrease in the measured and synthesized aortic systolic pressures than in the radial artery pressure. The synthesized aortic systolic pressure was less, by 6–8 mm Hg (SD 2–3) and the synthesized aortic diastolic pressure greater, by 4 mm Hg (SD 2). Despite these differences in pulse pressure, the synthesized waveform tracked the measured waveform before and during interventions.

Conclusions. By deriving an aortic waveform from the radial pulse, monitoring of left ventricular afterload can improve without more invasive means.

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Some health workers assume that peripherally measured systolic, diastolic and pulse pressures represent these pressure values throughout the arterial tree However, the aortic systolic and pulse pressures are usually less than those measured peripherally.[1-4] These differences in arterial pressures have been explained on the basis of wave reflection at peripheral sites.[5] The difference is increased with some, but not all, vasodilating agents,[6 7] in shock and with tachycardia.[8] Such effects are usually hidden, since we lack simple, practical methods to measure central systolic pressure. Hence, the cardiac consequences of relatively large changes in proximal aortic pressure are often unseen and neglected. Furthermore, the cuff sphygmomanometer sets numbers to the extremes of arterial pressure but carries no information about the dynamics of arterial pressure during the cardiac cycle. To overcome this lack of information, new non-invasive methods have evolved to generate the ascending aortic pressure wave from the radial or brachial pressure wave.[9] One such system, SphygmoCor™ (PMV Medical, Sydney) synthesizes the ascending aortic pressure wave from the radial pressure

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[†] *Declaration of interest* Professor M. F O'Rourke is a Director of PWV Medical, Sydney. PWV Medical provided funds and facilities for analysis of the data, and markets apparatus that uses the methods used in this study.

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wave through a generalized transfer function so that cardiac and vascular interactions can be calculated.[10–14] A transfer function is a mathematical description of the change in pulsatile phenomena between two sites, expressed in the frequency domain in terms of modulus and phase, and is widely used in engineering sciences. A generalized transfer function is a transfer function that can be used in different persons under different circumstances.[9 15] This is the first formal investigation of the SphygmoCor technique applied to an intra-arterial radial waveform. We chose to study elderly patients scheduled for percutaneous transluminal coronary angioplasty (PTCA) since they have a non-compliant arterial system. This increases wave reflection, induces systolic hypertension and is thus an additional cardiac risk factor during major surgery. Perioperative monitoring of such patients includes a radial arterial cannula. The aim of this study was therefore to compare the synthesized aortic (SA) pressure wave derived from the measured intra-arterial radial (MR) waveform by comparing SA with the directly and simultaneously measured (catheter-tip manometer) ascending aortic pressure wave (MA). Our protocol included control recordings, and recordings during the Valsalva manoeuvre, vasodilatation with midazolam and nitroglycerin, followed by a second Valsalva manoeuvre.

Methods

The study was approved by the Sahlgrenska University Hospital ethics committee and informed consent was obtained from each patient. Twelve patients with angina pectoris, 8 men and 4 women, mean age 67 years (range 62–76 years), scheduled for PTCA were included. They all had left ventricular ejection fractions greater than 50% calculated at echocardiography or previous coronary angiography and none had any clinical evidence of heart failure. The measurements were done in the morning, fasting, before the PTCA. Patients treated with β-receptor antagonists (*n*=8) received their regular morning dose. No other drugs were administered before the study.

Aortic recordings were obtained with an 8F Cordis catheter-tip manometer with a pressure interface (Sentron, The Netherlands).[16] The catheter has a flat frequency response up to 180 Hz. Following local anaesthesia, the catheter was introduced from the femoral artery and positioned in the ascending aorta just proximal to the brachiocephalic trunk. The right radial artery was cannulated with a 45 mm Ohmeda (Swindon, UK) arterial cannula (inner diameter 1.0 mm) and connected to an external pressure transducer (Peter van Berg, Kirschseeon, Germany) by high-pressure tubing that was only 10 cm long to minimize signal distortion. When tested in our laboratory according to Gardner[17] this pressure measurement system had a natural frequency of 25 Hz and a damping coefficient of 0.35–0.5. This implies that the signal has minimal distortion. The Siemens Sirecust 1281 cardiovascular monitoring system (Siemens Medical Electronics Inc., Danvers, MA) that we used had a high-pass filter with a cut-off at 16 Hz.

The Valsalva manoeuvre was accomplished by a prolonged forced exhalation through a facemask with an attached resistance. Airway pressure was measured at the mask and a positive airway pressure of 10–70 mm Hg was generated. In relation to the Valsalva manoeuvres, measurements of systolic and diastolic pressures were made on individual pulse waves because the SphygmoCor software is based on averaging 8 s of stable pulse waves. Pressures were measured immediately before and during the peak effect of the manoeuvre, with arterial pressure at its nadir.

All signals (ECG, radial arterial, aortic and airway pressures) were digitized (MP 100, Biopac, Cal., USA) at 200 Hz and processed in the data acquisition software (Acqknowledge, Biopac, USA). Data were later processed off-line in the SphygmoCor 128 Hz. The generalized transfer function used by SphygmoCor is based on data from Karamanoglu *et al.*,[11] who studied patients with coronary artery disease. This is virtually identical to the generalized transfer function described by Chen *et al.*[9] During each period of measurement a recording of a stable 8 s wave train was ensemble-averaged by the SphygmoCor into a single waveform for each of MA, SA and MR, and timing and pressure data (systolic, diastolic and end systolic pressures) calculated. End systolic pressure (ESP) was determined by identification of the cardiac insicura through use of differentials. Indices were: time–pressure area during systole (As) and diastole (Ad) and their ratio (Ad/As), systolic pressure augmentation index (AI), which defines the relation between the first (P1) and second (P2) systolic shoulder/peak (i.e. AI=100×(P2–P1)/pulse pressure).[18 19]

Since the exact sagittal position of the aortic catheter in relation to the zero level of the external pressure transducer was unknown, mean values of both synthesized and measured pressures were set to be the same as in the pressure in the radial artery. All aortic pressure values were then adjusted arithmetically.

Experimental plan

Measurements started with a control period after 20 min of rest (*n*=12), followed by the first Valsalva manoeuvre (*n*=11). We then gave midazolam 1–2 mg i.v. and took recordings after 3–5 min (*n*=12). Immediately after this, nitroglycerin 0.25–0.5 mg was administered sublingually. Two sets of recordings were then taken, reflecting both early (after 2 min, *n*=11) and maximal nitroglycerin effect (after approximately 5 min, *n*=11). Statistics and Bland–Altman plots were calculated using the mean of these two measurements. With nitroglycerin effect still at its peak, a second Valsalva manoeuvre was performed (*n*=15).

Statistical analysis

Data are presented as mean (SD). Data were compared using paired Student's *t* test. Individual data from all interventions are shown in Bland–Altman plots.[20] ANOVA for repeated measurements was used to test the consistency of the differences between MA and SA, and between MA and MR during the different pharmacological interventions, with Tukey's post-hoc test.

Results

The Valsalva manoeuvre was studied on 27 occasions, 12 before any drugs were administered and 15 after the administration of midazolam and nitroglycerin (Figs 1 and 2). During the Valsalva manoeuvre systolic pressure decreased by 51 (22) mm Hg in MA. The difference in systolic pressure between MR and MA increased from 9 to 14 mm Hg during the Valsalva manoeuvre, and the difference between systolic pressure in SA and MA disappeared during the peak effect, from 4 to 0 mm Hg. The response to the Valsalva manoeuvre was similar before and after the administration of nitroglycerin.

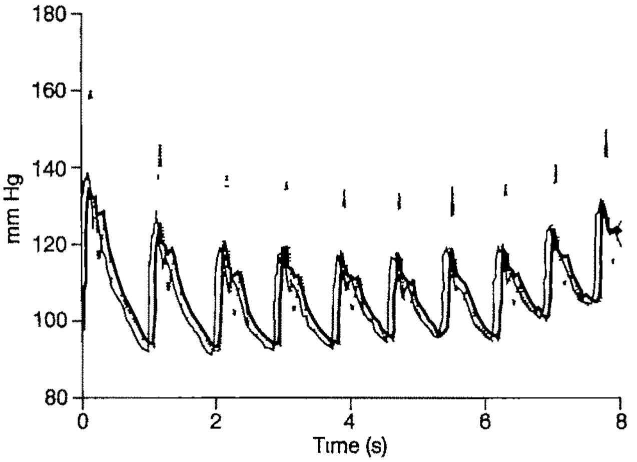

Fig 1 An example of pulse waves during peak effect of the Valsalva manoeuvre, displaying the close correlation between measured (thin line) and synthesized aortic (SA; bold line) waveforms compared with the radial waveform (dotted line) Since the SA waveform is constructed from the radial wave they appear synchronous in time.

The decrease in systolic and mean arterial pressure induced by midazolam was accentuated by nitroglycerin (Table 1). However, nitroglycerin caused a more pronounced fall in systolic pressure and pulse pressure in the aorta (MA) than in the radial artery (MR). Ad/As was markedly increased only by nitroglycerin, with a more pronounced decrease in As. The latter was associated with decreases in systolic augmentation in MA, SA and MR, and with a typical pointed appearance of the radial pulse wave (Fig. 3). Heart rate was not significantly affected by midazolam or by the addition of nitroglycerin.

Changes in pulse waves induced by changes in stroke volume and wave reflection are shown as changes in systolic augmentation and pulse wave contour and have been classified by Murgo *et al.*[18] Before administration of any drug, true aortic pulse waves (MA) were monophasic (Fig. 3) and the SphygmoCor software could not detect inflection during systolic upstroke in five out of 12 patients, meaning that these pulse waves were not classified. The remaining seven patients were classified as Murgo type A, which implies an early systolic shoulder followed by an augmented late systolic peak (as seen in the SA waveforms in Fig. 3). Data from individual patients are displayed in Table 2. When arterial pressure was affected by midazolam and later by nitroglycerin, systolic augmentation in MA decreased (Table 1) and early systolic inflection points could be detected by the software in all but one of 34 MA pulse waves. (All 12 patients received midazolam, all but one received nitroglycerin, and the nitroglycerin effect was measured twice, i.e. 12+11+11=34.) In the SA pulse waves early systolic inflection was detected in 45 out of 46 recordings (including control measurements). Thus the Murgo classification was identical between MA and SA in 92% (36 out of 39 recordings). Accordingly, because of failure of detection of systolic inflection, AI could not be

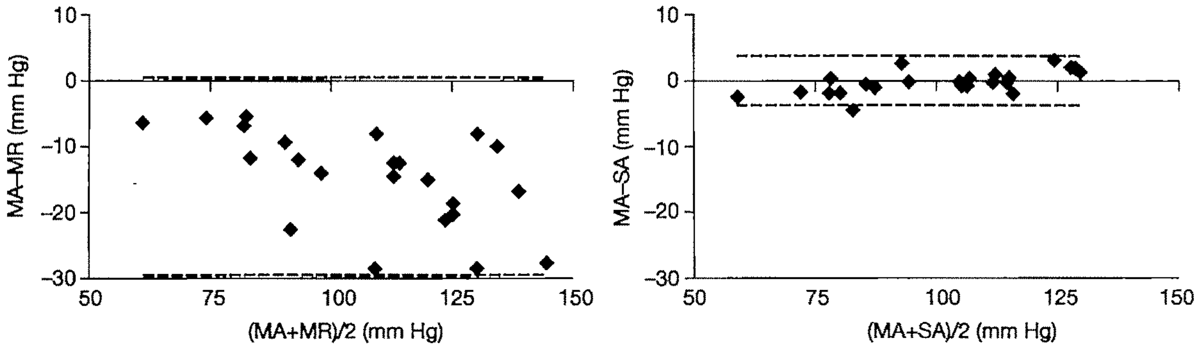

Fig 2 Bland–Altman plots showing the differences between systolic pressure during Valsalva in the measured aortic waveform (MA) and radial waveform (MR), left panel, and the differences in systolic pressure during Valsalva between MA and synthesized aortic waveform (SA), right panel The dotted lines display mean and 2SD.

Table 1 Pressure and pulse wave variables during control, midazolam and nitroglycerin MR, measured radial pressure waveform, MA, measured aortic pressure waveform; SA, synthesized aortic pressure waveform, Ad, diastolic time pressure area (integral), As, systolic time pressure area (integral), NS, not significant

	Waveform type	Control		Midazolam		*P* value	Nitroglycerin		*P* value
		Mean	SEM	Mean	SEM	M *vs* C	Mean	SEM	N *vs* M
Mean arterial pressure (mm Hg)	MR	109	3	97	3	<0.001	93	4	<0.05
Systolic pressure (mm Hg)	MR	169	4	147	5	<0.001	141	5	<0.05
	MA	168	4	145	4	<0.001	133	6	<0.01
	SA	160	4	138	5	<0.001	126	5	<0.01
Diastolic pressure (mm Hg)	MR	72	2	66	3	<0.01	66	3	NS
	MA	71	2	64	3	<0.01	64	3	NS
	SA	74	2	68	3	<0.01	68	3	NS
Systolic pressure difference (mm Hg)	MR–MA	1	1	2	1	NS	8	2	<0.001
	MR–SA	9	1	9	1	NS	14	2	<0.01
End systolic pressure (mm Hg)	MR	118	3	104	4	<0.001	96	3	<0.01
	MA	137	4	117	4	<0.001	108	4	<0.01
	SA	137	4	120	4	<0.001	112	4	<0.005
Heart rate (beats min^{-1})		61	2	63	3	NS	67	3	NS
Ad/As	MR	118	6	121	5	NS	150	7	<0.01
	MA	127	5	128	5	NS	137	7	<0.05
	SA	136	6	139	6	NS	150	7	<0.05
Augmentation index (%)	MR	−1	3	−8	3	<0.001	−18	3	<0.05
	MA	40	2	36	3	<0.05	25	2	<0.001
	SA	36	2	34	2	<0.05	21	2	<0.001

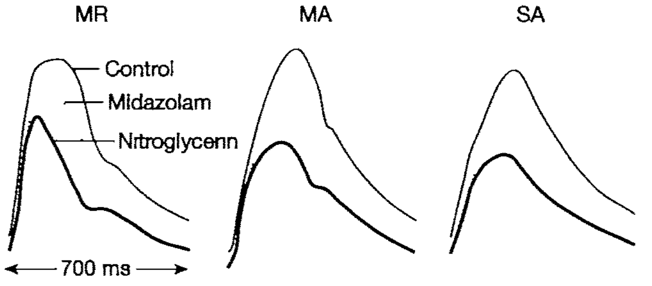

Fig 3 Ensemble averaged pulse waves from all points of measurement in all patients The control period is represented by a thin line, midazolam by a dotted line and nitroglycerin by a bold line Note the disappearance of the late systolic shoulder and the minor decrease in systolic pressure in the radial artery during nitroglycerin, while both the synthesized and measured aortic pulse waves display a marked and uniform fall in systolic pressure, and the same wave contour.

calculated in 13% of the MA, 4% of the SA and 9% of the MR registrations. ESP decreased, in parallel with the fall in systolic pressures, in MR, MA and SA.

Mean values of the differences between measured and synthesized aortic pulse waves (MA–SA) and between MA and radial pulse waves (MA–MR) are shown in Table 3. Analysis of variance for repeated measurements (not including the Valsalva manoeuvre) showed no changes in the differences between MA and SA for systolic and diastolic pressures, AI or Ad/As. The difference between ESP in MA and SA showed a minor but significant change (Table 3A) in the analysis of variance. When comparing the differences between MA and MR, however (Table 3B), ANOVA indicated *changes* in the differences concerning systolic pressure and ESP and Ad/As.

The SphygmoCor SA pulse wave consistently underestimated aortic systolic pressure by 6–8 mm Hg (SD 2–3) and overestimated aortic diastolic pressure by 4 mm Hg (SD 2) (Table 3A). SA followed the decrease in aortic systolic pressure when nitroglycerin was added to midazolam, whereas the MR did not. Although the difference between systolic pressure in the radial artery and in the SA pulse wave (MR–SA) was larger than the 'true' difference (MR–MA), both gradients increased similarly during nitroglycerin (Table 1).

Systolic AI in SA approximated that in MA. The magnitude of the *changes* in pulse wave parameters induced by midazolam and the further addition of nitroglycerin were always similar in the measured and synthesized aortic pulse waves (Table 1).

Individual values are shown as Bland–Altman plots in Fig. 4A–D. Figure 4A shows a consistent underestimation of the SA systolic pressure compared with MA and a large scatter in MR compared with MA systolic pressures during nitroglycerin. The resemblance between MA and SA is good with regard to ESP and AI (Fig. 4B–C). SA consistently underestimated systolic and overestimated diastolic pressure areas compared with MA.

Discussion

The SA pressure waveform derived by SphygmoCor closely followed the MA waveform beat by beat and also during changes in arterial pressure induced by vasodilators or the

Table 2 Individual patient values for measured and synthesized aortic systolic pressures and augmentation indexes. MA, measured aortic pressure waveform; SA synthesized aortic pressure waveform; C, control; M, midazolam; N, nitroglycerin; NS, not significant

Gender/age	β blocker	Systolic pressure						Augmentation index					
		MA			SA			MA			SA		
		C	M	N	C	M	N	C	M	N	C	M	N
Male, 66	1	193	159	164	182	150	154	46	37	23	34		21
Male, 67	0	177	142	125	168	137	121	39	25	20	22	21	10
Female, 69	1	152	137	127	146	129	121	44	43	29	39	32	28
Male, 68	1	168	151	127	161	144	124	44	39	25	33	32	22
Male, 64	1	162	132	118	153	122	110		44	28	37	38	32
Male, 62	0	161	140	124	153	131	118		46	31	34	34	12
Female, 68	1	182	151	153	180	143	143	36	28	25	36	30	20
Male, 62	1	185	173	160	176	166	152		41	21	40	34	33
Male, 69	0	173	162	138	165	156	131	28	27	13	30	30	13
Female, 69	1	157	124	115	149	118	111		44	34	41	38	22
Female, 67	0	142	123		133	116		42	13		47	43	
Male, 76	1	164	144	110	157	142	110		47	31		40	26

Table 3 (A) Differences between measured (MA) and synthesized (SA) aortic pressure waveforms, and (B) differences between MA and measured radial (MR) pressure waveforms. Differences between MA and SA, and between MA and MR were tested using the Student's paired *t* test. Changes of the differences were tested using ANOVA (see text). The Valsalva manoeuvres were not included in the ANOVA. Ad, diastolic time pressure area (integral); As, systolic time pressure area (integral); NS, not significant

A	Control			Midazolam			Nitroglycerin			Valsalva		
	MA–SA	SD	*P* value	MA–SA	SD	*P* value	MA–SA	SD	*P* value	MA–SA	SD	*P* value
Systolic pressure (mm Hg)	8	2	<0.0001	7	2	<0.0001	6	3	<0.0001	0.1	1.8	NS
Diastolic pressure (mm Hg)	–4	2	<0.0001	–4	2	<0.0001	–4	2	<0.0001	–3.4	2.2	<0.0001
End systolic pressure (mm Hg)	–1	4	NS	–3	3	<0.001	–3	3	<0.01			
Augmentation index (%)	5	8	NS	2	12	NS	4	8	NS			
Ad/As (%)	–9	6	<0.001	–11	8	<0.001	–13	4	<0.0001			

B	Control			Midazolam			Nitroglycerin			Valsalva		
	MA–SA	SD	*P* value	MA–SA	SD	*P* value	MA–SA	SD	*P* value	MA–SA	SD	*P* value
Systolic pressure (mm Hg)	–1	5	NS	–2	4	NS	–8	5	<0.001	–14.4	7.5	<0.0001
Diastolic pressure (mm Hg)	–1	2	<0.05	–2	2	<0.01	–2	1	<0.001	–2.3	2.3	<0.0001
End systolic pressure (mm Hg)	19	5	<0.0001	13	4	<0.0001	12	7	<0.0001			
Augmentation index (%)	44	11	<0.0001	44	15	<0.0001	44	14	<0.0001			
Ad/As (%)	9	4	<0.0001	7	7	<0.005	4	6	NS			

Valsalva manoeuvre. This was also true for ESP, which is an important but normally difficult value to measure when ventricular/vascular interactions are being studied.[21]

Pressure

The aortic pulse pressure was underestimated using the SphygmoCor software. This was largely the result of a discrepancy in systolic pressure. The underestimation may be explained in several ways. A small but systematic bias was introduced in the study by setting measured and SA mean pressures identical to radial mean pressure. Normally the aortic mean pressure should be 1–3 mm Hg higher than the radial mean pressure.[4] More importantly, the generalized transfer function used by the SphygmoCor is based on data from a younger population (mean age 54 years)[11] than investigated in the present study (mean age 67 years). In younger individuals, pulse pressure amplification along the arterial tree results in a higher peripheral systolic pressure. The less compliant arterial system of an elderly individual will equalize peripheral and central systolic pressure. Indeed, similar resting aortic and radial systolic pressures were observed in the present study. Furthermore, the generalized transfer function is based on pooled data including pressure waveforms at rest, as well as during infusion of nitroglycerin.[11] Individualized transfer functions have been evaluated previously[9] and were found to be only marginally superior to the generalized transfer function in reconstructing central pressures. Further validation studies should involve young individuals with normal and compli-

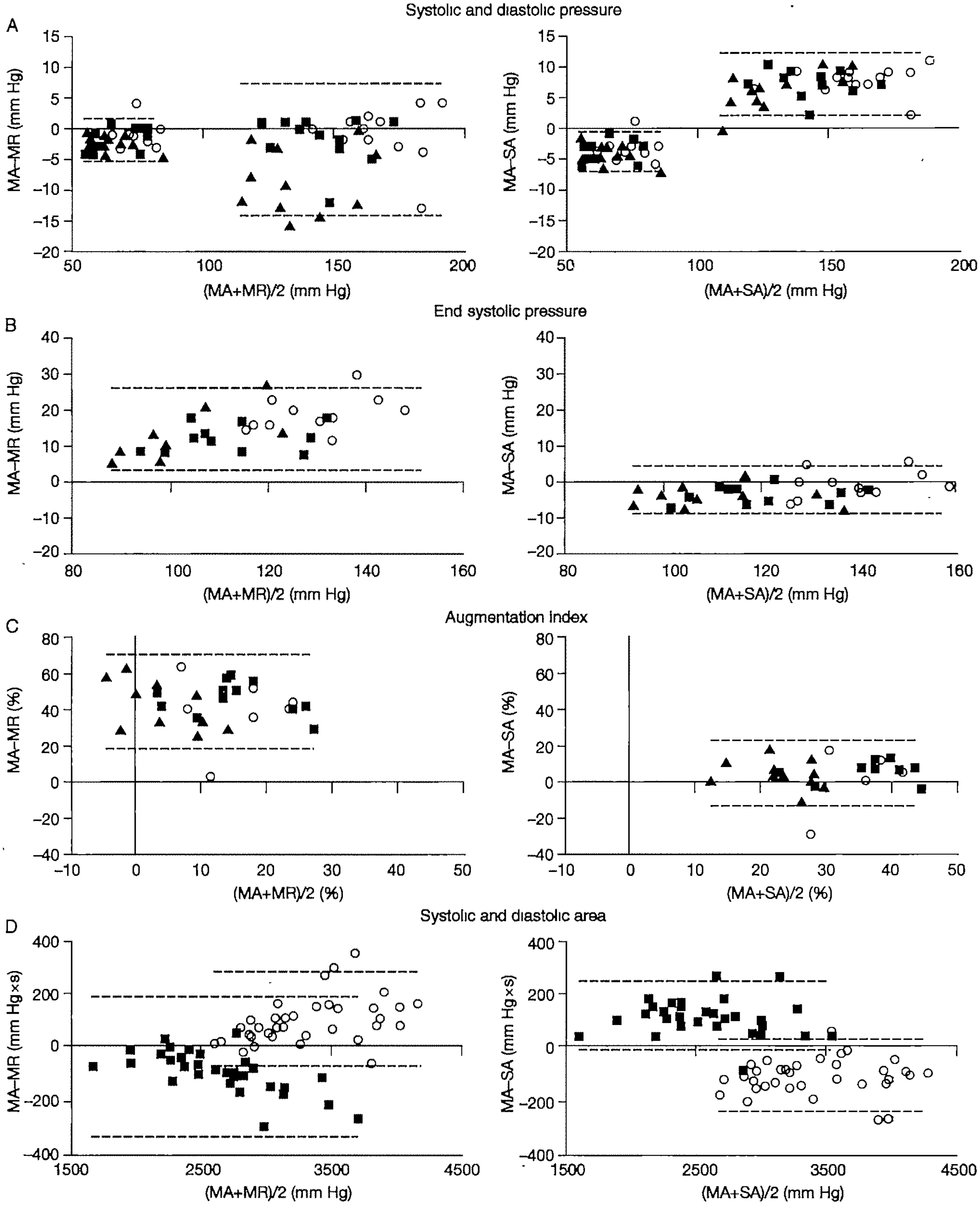

Fig 4 Bland–Altman plots displaying the differences between measured aortic waveform (MA) and measured radial waveform (MR) (left panel) and between MA and synthesized aortic waveform (SA) (right panel) for systolic and diastolic pressures (A), end systolic pressures (B); augmentation index (C); and systolic and diastolic areas (D). True aortic systolic pressure was underestimated by SA and diastolic pressure overestimated, but variation in systolic pressure, especially with nitroglycerin, was reduced compared with MR In A, B and C, circles indicate controls, squares indicate midazolam and triangles indicate nitroglycerin intervention. In D, squares indicate systolic area and circles indicate diastolic area. Dotted lines display mean and 2SD

ant arterial vasculature. It can be argued that the fluid-filled radial catheter system could introduce damping and thus lower the pulse pressure in the SA wave. This seems unlikely, however, since the extremely short fluid-filled radial system had a natural frequency and damping coefficient well above monitoring standards.[17] Longer extensions have so far not been validated. About 90% of the power in the aortic pressure is within the first three harmonics[10] and these are unlikely to be affected by the length of the tubing. Longer extensions, however, will decrease the natural frequency of a fluid-filled external system, making it susceptible to false amplification during tachycardia. In such a system a high heart rate may introduce errors which were not encountered in the present study.

Waveform

A monophasic systolic peak was observed in the aortic pressure waveform. This pattern differs from the original work by Murgo *et al.*,[18] who describe a late systolic peak as a result of the reflected pressure wave (type A waveform), considered typical in elderly or hypertensive individuals. Again, differences in the composition of study populations may explain the different waveforms observed. The study by Murgo *et al.* was of a population with a mean age of 34 years, compared with 67 years in this investigation. The pressure wave reflection in an elderly group of individuals with a less compliant arterial vascular tree is probably so fast that the incident wave meets and blends with the reflected wave very early in systole.

The waveform can be described as a supply/demand relationship. The area under the diastolic part of the pulse wave, Ad, is hence divided by the systolic area, As (i.e. Ad/As), where Ad represents the potential for coronary perfusion enabling the cardiac workload, As.[22] Interestingly, in our study, this relationship was altered only by nitroglycerin, despite a more pronounced decrease in systolic pressure during midazolam. This shows that nitroglycerin can decrease not only stroke volume but also pulse wave reflection.

The AI indicates vascular stiffness, reflecting both structural vascular changes as in hypertension or diabetes[23] and pharmacologically induced dynamic changes in pulse wave reflection where the second systolic peak represents the reflected pressure wave.[7] Perhaps in patients with intact endothelial function[24] changes in AI could indicate depth of anaesthesia and sympathetic tone.

Clinical implications

We found that systolic pressure and AI from a radial cannula should be used with caution even as a rough estimate of aortic data (Fig. 4, left-hand panels). Whereas midazolam did not affect the gradient between radial and aortic pressures, the addition of nitroglycerin did (Fig. 3). With midazolam the radial and aortic pulse wave changes suggested that midazolam elicits an arteriolar vasodilatation without major changes in stroke volume. Midazolam and nitroglycerin in combination affected the pulse waves in the same way as when nitroglycerin was given alone, which suggests dilatation of small arteries and reduced stroke volume.[7] The Valsalva manoeuvre decreased transmural aortic pressure and pulse wave velocity and reduced stroke volume, with increased heart rate and vasoconstriction. The net effect of these changes on pulse wave reflection was a delay of the reflected wave into diastole.[5] In the present study the agreement between measured and synthesized aortic pressure improved during the Valsalva manoeuvre. Speculatively, both reduced stroke volume and increased heart rate during the Valsalva manoeuvre could lower central systolic pressure more than radial pressure, similar to the effects of nitroglycerin.[7] If this difference in pressure reduction equals the underestimation of aortic systolic pressure by the SphygmoCor, measured and SA aortic pressures would coincide. These observations are similar to those made by Chen *et al.*[9]

The information contained in arterial pressure waveforms is probably underused in anaesthesia and intensive care. The present study shows that if the radial pulse wave is continuously translated into an aortic pulse wave, the level of monitoring can improve without more invasive means. Continuous monitoring of aortic pressure and waveform gives a better estimate of left ventricular afterload than does radial monitoring and is of importance in volume and drug therapy. There is no reason why the detailed information contained in the arterial pressure waveform should be overlooked by the anaesthetists and intensivists who are regularly confronted with arterial pressure waveforms. Further studies should assess pulse wave reflection and late systolic augmentation. The present study illustrates the benefits and possible pitfalls of using a generalized transfer function in elderly patients. The SA pulse wave will be damped, causing a moderate but consistent underestimation of pulse pressure and systolic time–pressure area. The underestimation of systolic pressure is not seen with an increased intrathoracic pressure.

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Glucose, insulin and potassium for heart protection during cardiac surgery

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Background. Coronary artery bypass grafting with hypothermic cardiac arrest and cardiopulmonary bypass (CPB) is associated with myocardial injury. Our study investigated whether an infusion of glucose, insulin and potassium (GIK) during elective coronary artery bypass surgery decreases myocardial cell death.

Methods. We measured cardiac troponin I (cTnI), a myofibrillar structural protein, which is a sensitive and specific indicator of myocytic injury. With ethics committee approval, 42 patients were enrolled into a randomized, prospective, double-blinded study. In the GIK group, 500 ml of 50% dextrose solution containing 100 IU insulin and potassium 80 mmol was infused at the rate of 0.75 ml kg^{-1} h^{-1}. Patients in the non-GIK group received 5% dextrose solution at the same rate. Arterial blood samples were taken before induction of anaesthesia, after removal of the aortic clamp and 6 and 12 h after CPB.

Results. In both groups there was an increase in cTnI concentration ($P<0.05$), which was greatest about 6 h after CPB. At no time did the cTnI concentration differ between the two groups.

Conclusion. The results suggest that GIK does not decrease the irreversible myocardial damage associated with routine coronary artery bypass surgery.

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The use of glucose–insulin–potassium (GIK) for cardiac protection was first described 25 yr ago.[1] New interest in the possible protective effect of GIK in patients with myocardial infarcts followed the 1998 Estudios Cardiologicos Latinoamerica (ECLA). In this multicentre study, a high-dose regimen of GIK (25% glucose solution containing insulin 100 IU and potassium 80 mmol per litre) infused at 1.5 ml kg^{-1} h^{-1} in patients with acute myocardial infarct significantly reduced mortality in patients given thrombolytic therapy or angioplasty.[2] The mechanism was not clear, but one proposed mechanism was reduction in cell death and infarct size.

During ischaemia, the heart has limited oxidative reserve and energy-rich phosphates are steadily depleted. In hypoxia, GIK may protect myocardial tissue by maintaining normal carbohydrate and fatty acid metabolism and thus cell function. The effects of GIK and its influence on myocyte metabolism, specifically during ischaemia and reperfusion, are complex. The protective effect of GIK on the functional recovery of the heart has been investigated extensively.[3–6]

Cardiac troponin I (cTnI) is a myofibrillar structural protein, and the cardiac isomer is specific to heart muscle. cTnI is a more reliable marker of irreversible myocardial cell damage than creatine kinase MB.[7–10] Surgery using cardiopulmonary bypass (CPB) with hypothermic cardiac arrest is associated with damage to the heart despite improvements in surgery, anaesthesia and the technique of CPB.[11 12] We examined whether an intraoperative infusion of GIK could reduce irreversible myocardial cell damage, using cTnI as a marker of myocyte injury.

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Table 1 Patient characteristics. Values are mean (SD), number (%) or ratio

	GIK group (19 patients)	**Non-GIK group (20 patients)**
Age (yr)	64.3 (9.9)	66.3 (10.4)
Gender ratio (M:F)	19:0	15:5
Bypass time (min)	80.3 (22.3)	69.5 (20.3)
Cross-clamp time (min)	50.7 (13.7)	45.2 (12.4)
Hypertension	17 (90%)	18 (90%)
Hypercholesterolaemia	14 (74%)	13 (65%)
Preoperative ejection fraction <45%	9 (47%)	3 (15%)
Previous myocardial infarction	10 (53%)	8 (40%)

Methods

With local ethics committee approval and informed patient consent, we conducted a double-blinded prospective randomized study of 42 patients scheduled for elective coronary artery bypass grafting. Three patients were excluded from analysis, two because of incomplete sampling and one because of missing randomization. All patients who electively received at least two bypass grafts were included in the study. Exclusion criteria were an abnormal creatinine concentration and type 1 and type 2 diabetes. Assessment of ejection fraction was part of the routine preoperative evaluation.

Patients received either 50% glucose 500 ml containing insulin 100 IU and potassium 80 mmol at a rate of 0.75 ml kg^{-1} h^{-1} (GIK group) or an equivalent rate of 5% dextrose (non-GIK group), given into a central vein. The infusion started immediately after induction of anaesthesia and stopped at the end of surgery. Blood glucose was measured hourly and insulin was given according to a sliding scale to maintain blood glucose between 4 and 10 mmol litre^{-1}. Potassium was added to achieve a plasma concentration of 4–6 mmol litre^{-1}. Peripheral arterial blood samples were collected for cTnI analysis before induction of anaesthesia, after removal of the aortic cross-clamp and 6 and 12 h after CPB.

Surgical and anaesthetic technique

A standardized anaesthetic technique was used for all patients. Premedication consisted of oral temazepam 20 mg and ranitidine 150 mg. Anaesthesia was induced with fentanyl 10–15 μg kg^{-1} and propofol 2 mg kg $^{-1}$. A single dose of vecuronium 0.15 mg kg $^{-1}$ was used for muscle relaxation. Anaesthesia was maintained with 30% oxygen in nitrous oxide and isoflurane before CPB. End-expiratory isoflurane concentration was held between 0.6 and 0.8%. Thereafter, a propofol infusion of 100–350 mg h^{-1} was used to maintain anaesthesia until transfer to the recovery area. Supplementary i.v. fentanyl was administered according to the discretion of the anaesthetist up to a maximum of 500 μg. Inotropic drugs were administered only when required to facilitate separation from CPB.

The same surgeon operated on all patients. Cardiopulmonary bypass was achieved with a roller pump and membrane oxygenator with mild hypothermia of 32°C. Multiple anterograde doses of St Thomas' cardioplegia solution in cold (6°C) oxygenated blood were infused for myocardial preservation. St Thomas' solution contains magnesium chloride BP 3.253 g, potassium chloride BP 1.193 g and procaine hydrochloride BP 272.8 mg in 20 ml. CPB time, aortic cross-clamp time and reperfusion time were noted. Mean arterial pressure was maintained between 50 and 60 mm Hg either by adjusting pump flow or with small boluses of phenylephrine. Anticoagulation was with heparin 300 IU kg^{-1} and further doses to maintain an activated clotting time greater than 480 s.

Blood sampling and laboratory analysis

Blood samples were taken into tubes without anticoagulant and centrifuged at 2500 *g* for 20 min. The serum obtained was then stored at –70°C until analysis.

Quantitative cTnI analysis was performed using the Bayer Immuno-1 assay (Bayer, Leverkusen, Germany), a heterogeneous sandwich magnetic separation system using mouse monoclonal and goat polyclonal anti-cTnI antibodies. Both antibodies were directed to epitopes at the centre of the cTnI molecule. The detection antibodies were labelled with alkaline phosphatase and addition of substrate subsequently gives a colour change directly proportional to the cTnI concentration. The assay had a detection limit of 0.1 μg litre^{-1} and an analytical range up to 200 μg litre^{-1}. The interassay coefficient of variation was 6% at a concentration of 0.2 μg litre^{-1}, which was the manufacturer's recommended clinical discriminatory level for myocardial injury (cTnI $\geqslant$0.9 μg litre^{-1} is considered diagnostic of acute myocardial infarction).

Statistical analysis

A power analysis showed that 17 patients in each group would be required to detect a mean difference of 0.9 (SD 0.8) μg litre^{-1} in cTnI concentration between the two groups at any of the time points with a power of 90% and a *P* value of 0.05. The cTnI data were assessed with the Shapiro–Wilk test of normality and were distributed asymmetrically. Non-parametric statistical tests were therefore used for cTnI analysis. The Mann–Whitney *U*-test was used to test for differences in cTnI concentration between groups at each time point. Changes in cTnI concentration over time within groups were assessed by Friedman analysis of variance (ANOVA) and the Wilcoxon signed ranks test. Fisher's exact test was used to determine whether there was a significant difference in the proportion of patients with a low ejection fraction (<45%) in the GIK group compared with the non-GIK group. Other categorical data, including all patient proportions (hypertension, hypercholesterolaemia, preoperative myocardial infarction, gender ratio), were

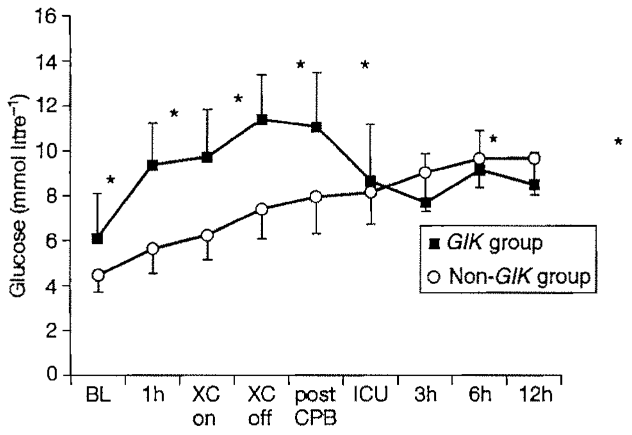

Fig 1 Glucose concentrations in the GIK group and non-GIK group Significant differences between groups are represented by asterisks ($P<0.05$). The graphs show mean concentrations and standard deviations (error bars) BL=baseline, 1 h=1 h after anaesthetic induction; XC=aortic cross-clamp, ICU=intensive care unit, 3, 6 and 12 h=3, 6 and 12 h after CPB

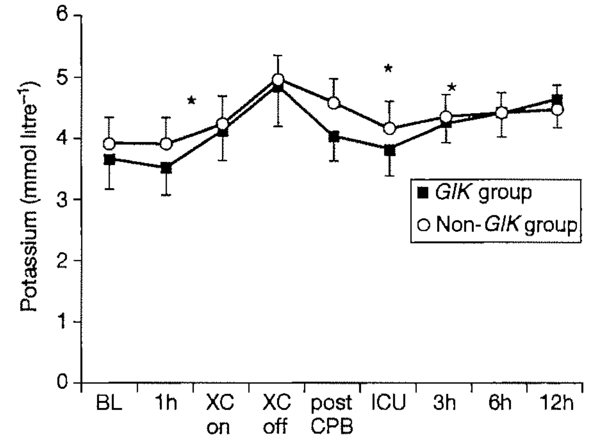

Fig 2 Potassium concentrations in the GIK group and non-GIK group Significant differences between groups are represented by asterisks ($P<0.05$) The graphs show mean concentrations and standard deviations (error bars) BL=baseline, 1 h=1 h after anaesthetic induction, XC=aortic cross-clamp, ICU=intensive care unit, 3, 6 and 12 h=3, 6 and 12 h after CPB.

also assessed with Fisher's exact test. The Mann–Whitney U-test was used to determine whether cTnI concentrations were greater in patients with low ejection fractions. The relationship between cross-clamp time and cTnI concentration was evaluated by Spearman correlation analysis. Patient age, CPB time, aortic cross-clamp time and blood glucose and blood potassium concentrations were normally distributed and were assessed with parametric statistical tests. Differences in these variables between the GIK and non-GIK groups were assessed with the unpaired t-test. Changes in potassium and glucose concentrations over time within groups were examined by ANOVA and paired t-tests. $P<0.05$ was regarded as significant for all tests. All statistical tests were carried out with Analyse-it software (Analyse-it, Leeds, UK).

Results

The groups were well matched for age and number of bypass grafts (Table 1). Four patients in group 1 and three patients in group 2 each had four grafts, and four in each group each received two grafts. All other patients had three coronary artery grafts with at least one internal mammary artery graft.

Randomization did not give an equal distribution of male and female patients. Ten patients (53%) in the GIK group and eight (40%) in the non-GIK group had suffered a previous myocardial infarct. Nine out of 19 patients (47%) in the GIK group had an ejection fraction less than 45%, compared with only three out of 20 (15%) in the non-GIK group ($P=0.06$). Mean operation times, cross-clamp times and CPB times did not differ between the two groups (Table 1).

Before operation, all patients were on beta-blockers and aspirin; the latter was stopped 5 days before surgery. A large number were also taking cholesterol-lowering medications and angiotensin-converting enzyme inhibitors

Inotropic support

In the GIK group, two patients received an epinephrine infusion and two patients required ventricular pacing to facilitate weaning from CPB. In the non-GIK group, one patient received epinephrine, one patient received dopamine 2 μg kg^{-1} min^{-1} and one patient needed ventricular pacing. No patient developed ECG changes after surgery that were suggestive of acute myocardial infarction.

Blood glucose concentration

None of the patients in the non-GIK group needed insulin to maintain blood sugar within the normal range. Twelve patients in the GIK group required additional doses of insulin. Blood glucose concentrations in the recovery phase were within the normal range in both groups (Figs 1 and 2). There were significant changes in blood concentrations in both the GIK and the non-GIK group over time ($P<0.05$). Glucose concentrations were greater in the GIK than in the non-GIK group during the entire intraoperative period ($P<0.05$). Three hours and 12 h after CPB, the blood glucose concentration was slightly lower in the GIK than in the non-GIK group ($P<0.05$).

There were significant changes in blood potassium concentration in both the GIK and the non-GIK group over time ($P<0.05$). Potassium concentration was lower in the GIK than in the non-GIK group from 1 h after induction of anaesthesia until the time of arrival in the intensive care unit ($P<0.05$) (Fig. 1).

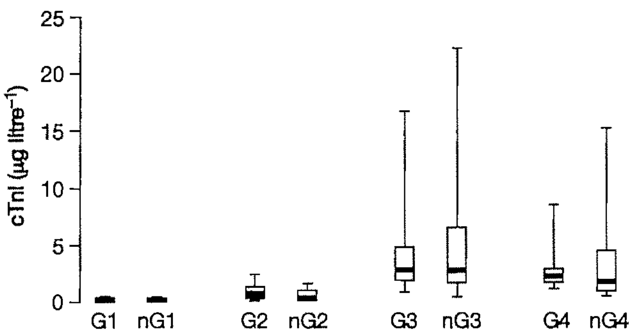

Fig 3 Box and whisker plots showing cTnI concentrations in the GIK (G) and non-GIK (nG) groups at four time points 1=baseline, 2=after aortic clamp removal; 3=6 h after CPB, 4=12 h after CPB. The boxes depict median values with interquartile ranges and the whiskers show the full ranges. In both groups, there was a significant ($P<0.05$) increase in cTnI concentration, with a peak concentration at time point 3. There was no significant difference in cTnI concentration between groups at any time

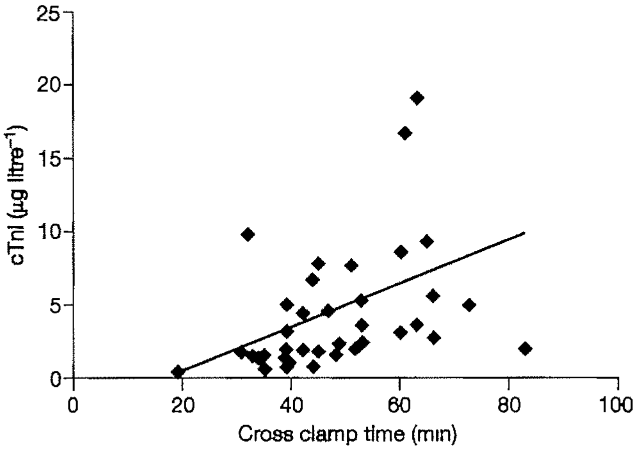

Fig 4 Correlation of cTnI concentration 6 h after CPB with cross-clamp time.

cTnI concentration (Fig. 3)

No patient had a significantly raised baseline cTnI concentration. In both groups there was an increase in cTnI concentration ($P<0.05$), in keeping with myocardial cell injury after cardiac surgery, which peaked about 6 h after CPB. At no time was there a significant difference in cTnI between the two groups ($P>0.05$) (Fig. 3). There was also no difference in cTnI concentration at any time point between patients with low and those with normal ejection fractions ($P>0.05$). There was a strong correlation between cross-clamp time and peak cTnI concentration ($r_S=0.57$, $P<0.001$) (Fig. 4).

Discussion

Cardiac surgery with hypothermic cardioplegic arrest causes some myocardial cell death, even in patients with no ECG changes and uneventful recovery.[13] Perioperative myocardial infarction is a clinically recognizable form of such damage and has an adverse effect on outcome.[12]

There is reason to believe that GIK infusion should aid recovery of the heart and decrease ischaemic injury during cardiac surgery using bypass. The possible benefits of GIK include the following.

(i) *A glycogen-sparing effect* by the supply of substrate to the cells during ischaemia.[4 5]

(ii) *Increased ATP synthesis.* During hypoxia there is depletion of energy-rich phosphates such as ATP, and glycolysis is important in the maintenance of myocardial viability.[14] ATP produced by oxidative phosphorylation is used preferentially to support myocyte contractile activity by supplying energy to the actin–myosin-ATPase.[15] Under normal circumstances, oxidative metabolism of free fatty acids is the predominant energy source for the myocardium. After reperfusion, oxidative metabolism of free fatty acids resumes but seems to be reduced after ischaemia.[6 14 16] Bunger and colleagues showed that, during the change from anaerobic to aerobic metabolism, glycolytic activity is critical for functional recovery of the heart and GIK could serve as a substrate.[17]

(iii) *Maintenance of sarcoplasmic reticulum function and calcium homeostasis.* Another explanation for a protective role of GIK is a possible compartmentation of glycolytic and oxidative ATPase.[15 18] This renders ATP derived from glycolysis vital for the recovery of the sarcoplasmic reticulum (SR) function after hypoxia. In a study conducted by Xu and colleagues,[15] sarcoplasmic reticulum vesicles from skeletal and cardiac muscle were isolated to investigate whether the energy derived from glycolysis was functionally coupled to active calcium transport in the SR. They found that the entire chain of glycolytic enzymes was associated with SR vesicles producing the ATP that was needed to maintain calcium pump function and thus SR membrane integrity. This suggests that there is functional coupling of glycolytic ATP to calcium transport and thus cell homeostasis.

(iv) *Free radical scavenging activity.*[19]

(v) *Reduction in free fatty acid concentration.* This is an insulin-related effect. Free fatty acids can harm cell membranes under hypoxic conditions, causing calcium overload, arrhythmias and cell death.[5 6]

(vi) *Decreased coronary artery resistance leading to increased myocardial perfusion.*[3 4]

We studied whether GIK decreases the amount of irreversible myocytic injury during coronary artery bypass grafting, in contrast to other studies, which assessed functional recovery of the heart.

To quantify the amount of myocardial damage perioperatively, we used cTnI, a sensitive and reliable marker for the detection of perioperative myocardial infarction.[11] The maximum value can be used to quantify the extent of myocardial cell death.[11 20] cTnI is accepted as a marker of perioperative risk stratification in cardiac risk patients undergoing non-cardiac surgery[21] and in patients undergoing coronary bypass grafting, because its concentration is related to the amount of irreversible cell injury. Higher perioperative concentrations are associated with more postoperative complications.[22] It has also been used to indicate underlying cardiac injury in intensive care patients[23 24] and to examine the benefit of different solutions and temperatures of cardioplegia.[25] The heart is most likely to sustain ischaemic injury when the aortic cross-clamp is applied. This is supported by our finding of a correlation between cross-clamp time and peak cTnI concentration.

In this study, despite the theoretical protective effects of GIK listed above and the reliability of cTnI as a marker of myocardial cell damage, no cardioprotective effect of GIK was observed. We did not find a significant difference in cTnI concentration between the two groups. The median values of both groups (Fig. 3) after 6 and 12 h showed that some myocardial death had occurred during surgery, supporting the findings of other studies,[13] but there was no difference between GIK- and non-GIK-treated patients. Before concluding that GIK confers no protective effect on the myocardium during CABG surgery, other possible reasons for our negative findings should be considered.

We used a high dose of GIK, as recommended in other studies,[16 26] but this was only given during surgery. It might be of more benefit if started before surgery and continued for 12–48 h after surgery, as suggested by other studies. Oldfield and colleagues examined the effect of GIK on complications of mitral valve replacement and demonstrated an increased myocardial glycogen content after an infusion of GIK 12 h before the operation.[27] This reduced complications after surgery, such as hypothermia and arrhythmia. Lazar and colleagues[28] found better cardiac performance and faster recovery from urgent coronary bypass grafting in patients with unstable angina given GIK infusion for 12 h after operation. These patients had greater cardiac output, a significantly lower incidence of atrial fibrillation (13.3 *vs* 53.3%; P=0.02) and a shorter stay in intensive care.

GIK might be beneficial in patients with decreased cardiac reserve, poor left ventricular function and/or cardiogenic shock. Patients with a high risk of death may be more likely to benefit from metabolic therapy.[29] Patients with insulin-dependent diabetes might benefit particularly from GIK, as shown in the DIGAMI study for patients with myocardial infarct.[30] A recent study by Lazar and colleagues found better cardiac performance and faster recovery after coronary bypass grafting in a group of 40 diabetic patients.[31] Postoperative GIK infusion for 48 h is of benefit in patients with refractory cardiac failure after hypothermic cardiac arrest for bypass grafting.[32 33]

Limitations of our study

It is possible that our study was too small and the groups too poorly matched to reveal the benefit of GIK. The different proportions of male and female patients in the GIK and non-GIK groups is unlikely to have influenced the results, but this possibility cannot be excluded. The possible influence of the ejection fraction was analysed retrospectively. Nine out of 19 patients in our GIK group and only three in the non-GIK group had an ejection fraction of less than 45% (P=0.06). The importance of the ejection fraction as a confounding factor is uncertain as there was no significant difference in cTnI concentration at any time point between patients with low and those with normal ejection fractions It remains speculative whether those patients in the GIK group with poor cardiac function would have had higher cTnI concentrations without GIK infusion. Differences in preoperative ventricular function can affect postoperative recovery but not necessarily the postoperative cTnI concentration, which specifically indicates myocardial cell death. It would be useful to conduct a larger study in diabetic patients or patients with decreased left ventricular function,[34] testing for an even smaller difference in cTn concentrations, and to relate cTnI to functional recovery of the heart. One problem with a high-concentration glucose infusion is hyperglycaemia during CPB, which could damage the brain and worsen neurological outcome. Hyperglycaemia may aggravate ischaemic brain injury[35] and be harmful after acute head injury.[36] The critical glucose concentration at which treatment should be initiated is not known.[37] A confounding factor is that high glucose concentrations may indicate severe head injury, as hyperglycaemia is a general stress response.[38] However, there is consensus that the blood glucose concentration should be maintained within the normal range.[37 38] Measuring glucose and potassium concentrations regularly is necessary. Blood glucose concentrations were higher in the GIK group implying that, in future studies, more insulin should be added to the glucose solution. Another concern is that increasing glycolysis can increase the concentrations of end-products such as lactate. Lactate accumulation is associated with inhibition of glycolysis and mitochondrial changes leading to cell damage, but in an animal study treatment with glucose did not affect the lactate concentration.[39]

Conclusion

We did not find that the use of GIK infusion during surgery reduced myocardial cell damage associated with cardiac surgery and CPB. However, it was associated with increased hyperglycaemia. As hyperglycaemia may worsen the neurological outcome, routine GIK infusions cannot be recommended until studies have been performed that demonstrate the value of this practice and determine which patients are most likely to benefit.

Acknowledgement

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Dexamethasone decreases the pro- to anti-inflammatory cytokine ratio during cardiac surgery

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Background. Cytokines regulate inflammation associated with cardiopulmonary bypass (CPB). Pro-inflammatory cytokines may cause myocardial dysfunction and haemodynamic instability after CPB, but the release of anti-inflammatory cytokines is potentially protective. We studied the effects of dexamethasone on pro- and anti-inflammatory cytokine responses during coronary artery bypass grafting surgery.

Methods. Seventeen patients were studied: nine patients received dexamethasone 100 mg before induction of anaesthesia (group 1) and eight patients acted as controls (group 2). Plasma levels of tumour necrosis factor (TNF)-α, interleukin (IL)-6, IL-8, IL-10 and IL-4 were measured perioperatively.

Results. TNF-α and IL-8 did not increase significantly in group 1 whereas they increased in group 2 to greater than preoperative values ($P<0.05$). IL-6 increased in both groups, with lower values in group 1 than in group 2 ($P<0.05$). IL-10 increased in both groups, with higher values in group 1 ($P<0.05$). IL-4 did not change in group 1 but decreased in group 2 compared with pre-induction values ($P<0.05$). After surgery, patients in group 2 had tachycardia, hyperthermia, a greater respiratory rate and higher pulmonary artery pressure, and a longer stay in the intensive care unit.

Conclusion. Dexamethasone given before cardiac surgery changes circulating cytokines in an anti-inflammatory direction. Postoperative outcome may be improved by inhibition of the systemic inflammatory response.

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Keywords: analgesics anti-inflammatory, steroid, dexamethasone; protein, cytokine

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Cardiac surgery and cardiopulmonary bypass (CPB) activate a systemic inflammatory response characterized clinically by changes in cardiovascular and pulmonary function. Significant morbidity is rare, but most patients undergoing CPB show some degree of organ dysfunction from activation of the inflammatory response. This systemic inflammatory response after CPB is thought to result from contact of cellular and humoral blood components with the synthetic material of the extracorporeal circulation, leucocyte and endothelial activation, caused by ischaemia and reperfusion or endotoxins, and finally by operative trauma.[1 2] Once started, the systemic inflammatory response is maintained by several factors, including cytokine production. The overproduction of the pro-inflammatory cytokines during CPB can harm the heart and other organs. For instance, they can significantly alter myocardial contractility,[3 4] and may contribute to the development of multi-organ failure.[5] The release of the anti-inflammatory cytokines during CPB may be protective by suppressing the production of pro-inflammatory cytokines.[6 7] The bal-

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ance of these pro-inflammatory and anti-inflammatory reactions may affect the extent of the inflammatory response and the clinical outcome in certain diseases.

Corticosteroids have been recommended during cardiac surgery to prevent haemodynamic instability after CPB and to inhibit the leucocyte and tissue plasminogen activator activity generated after the release of the aortic cross clamp, and thus improve the postoperative course.[8 9] The effect of steroid administration on the cytokine response during cardiac surgery has been described previously.[10 11] However, the evidence of steroid effect on the balance between pro-inflammatory and anti-inflammatory cytokines during cardiac surgery is still very limited. We studied the effect of a single dose of dexamethasone given before anaesthesia on the balance between pro-inflammatory and anti-inflammatory cytokines during coronary artery bypass graft (CABG) surgery. We measured circulating concentrations of the pro-inflammatory cytokines tumour necrosis factor (TNF)-α, interleukin (IL)-6 and IL-8 and the anti-inflammatory cytokines IL-10 and IL-4 in patients undergoing CABG with CPB, with and without dexamethasone pretreatment.

Patients and methods

Because of the cost of the assays, only 18 patients undergoing elective CABG surgery with CPB were randomized for this study. One patient in the control group was excluded from analysis because blood samples were incomplete The study was approved by the hospital ethics committee and all patients gave their informed consent. We excluded patients with severely impaired left ventricular function (ejection fraction <40%), pulmonary disease, severe systemic non-cardiac disease, renal or liver impairment, insulin-dependent diabetes, recent myocardial infarction (<6 weeks), infectious disease before operation, and those receiving corticosteroid or other immunosupressive treatment.

On the morning of the operation, patients were randomized to receive either dexamethasone 100 mg (group 1, n=9) or a placebo (group 2, n=9). This dosage was masked. Cardiac medication, including beta-adrenergic blocking agents, calcium-channel blocking agents and nitrates, was continued until the morning of surgery. All patients received lorazepam 40 μg kg^{-1} orally on the night before the operation and morphine sulphate 70 μg kg^{-1} i.m. and scopolamine 8 μg kg^{-1} i.m. 1 h before the operation. Anaesthesia was induced with sufentanil 2 μg kg^{-1} and midazolam 0.15 mg kg^{-1} and maintained with sufentanil 1.0 μg kg^{-1} h^{-1} and midazolam 0.12 mg kg^{-1} h^{-1}. Tracheal intubation was facilitated with pancuronium bromide 0.1 mg kg^{-1}. A bolus dose of sufentanil 0 5 μg kg^{-1} was given before skin incision. Patients were ventilated with oxygen/air (inspired oxygen fraction 0.5) with a tidal volume of 5–7.5 ml kg^{-1}, aiming at normocapnia.

The surgical procedure was median sternotomy and placement of internal mammary artery or saphenous vein grafts. Cardiopulmonary bypass was with a Cobe hollow-fibre membrane oxygenator. The circuit was primed with 1100 ml (500 ml gelofusine plus 500 ml Ringer's solution plus 100 ml mannitol). The CPB flow was maintained at 2.4 litre min^{-1} m^{-2}, and mild hypothermia of 32°C was accomplished. Cold cardioplegic solution was given after cross-clamping for myocardial protection (800–1000 ml initially and 200–300 ml after every 30 min through the aortic root and 100 ml after each distal anastomosis through the vein graft). Blood was sampled for measurement of TNF-α, IL-6, IL-8, IL-10 and IL-4 at the following times: before induction of anaesthesia (T0), after induction of anaesthesia and before skin incision (T1), before starting cardiopulmonary bypass (T2), after aortic declamping (T3), at the end of CBP (T4), 2 h after skin closure (T5), and 24 h after skin closure (T6). Samples were collected in tubes containing lithium heparin (VenoJect®, Terumo, Europe NV, Leuven, Belgium). The samples were immediately centrifuged at 1000 g, and the plasma was stored at −70°C until assays were performed. Enzyme-linked immunosorbent assays (ELISA; Immulite®, DPC, Los Angeles, USA) were used to measure TNF-α, IL-6, IL-8, IL-10 and IL-4. All assays were performed according to the manufacturer's instructions.

After completion of surgery, patients were transferred to the ICU, where standard care and processes were followed until discharge. The physicians and nurses in the ICU did not know which patients had received dexamethasone. Patients were weaned from mechanical ventilation when they were haemodynamically stable, responded to verbal stimulation, were completely rewarmed and when blood loss did not exceed 100 ml h^{-1}. Postoperative pain management was with piritramide 5–10 mg i v., given as necessary. Cardiovascular and respiratory values and temperature were recorded every 15 min before extubation and then hourly until discharge from the ICU. Length of stay in the ICU was also recorded. Patients were discharged from the ICU on the first morning that they were haemodynamically stable, had normal blood gases during spontaneous breathing and had satisfactory renal function. We reviewed each patient's records after discharge from the ICU and noted the minimum and maximum values of mean arterial pressure, heart rate, cardiac index, mean pulmonary artery pressure, respiratory rate, and temperature.

Statistical analysis

Calculations were performed on a personal computer using SPSS version 10.0. Data are presented as mean (SD) and cytokine concentrations as median (interquartile range). The groups were tested for differences using Student's t-test for continuous variables and Fisher's exact test for categorical variables. The Mann–Whitney U test was used to compare cytokine levels between the two groups at each time point.

Table 1 Characteristics of patient groups. Data are mean (SD) for continuous variables and numbers for categorical variables. NYHA, New York Heart Association

	Group 1 (*n*=9)	Group 2 (*n*=8)
Age (yr)	63 (10)	63 (7)
Height (cm)	174 (8)	174 (8)
Weight (kg)	84 (10)	85 (14)
Sex (m/f)	7/2	6/2
NYHA class (II/III/IV)	3/2/4	2/3/3
Smoker (no/yes)	4/5	6/2
Diabetes (no/yes)	9/0	6/2
Hypertension (no/yes)	3/6	6/2
Number of affected vessels	3.2 (0.8)	2.8 (0.7)

Table 2 Intra-operative characteristics of patient groups. Data are mean (SD)

	Group 1 (*n*=9)	Group 2 (*n*=8)
Number of grafts	4.3 (1.1)	4.3 (0.9)
Intraoperative blood intake (ml kg^{-1})	0.5 (1.5)	1.5 (3.0)
Intraoperative fluid intake (ml kg^{-1})	58 (6)	61 (15)
Total operation time (min)	252 (26)	220 (53)
Cardiopulmonary bypass time (min)	103 (18)	114 (19)
Aorta cross-clamping time (min)	69 (17)	74 (13)

Repeated measures analysis of variance together with Bonferroni adjustment was used for multiple within-group comparisons. In all cases a *P* value less than 0.05 was considered to indicate statistical significance.

Results

The two groups appeared similar in physical and preoperative clinical characteristics (Table 1). The intraoperative course was uneventful and intraoperative characteristics were comparable (Table 2). At all measurement times, serum TNF-α (Fig. 1) and IL-8 (Fig. 2) concentrations did not increase significantly above the pre-induction value in group 1 but in group 2 both cytokines increased at T3, T4 and T5 compared with pre-induction concentrations ($P<0.05$). TNF-α was significantly lower in group 1 than in group 2 at T4 (median [interquartile range] 8 [0–9] *vs* 80 (11–335) pg ml^{-1}; $P<0.05$) and T5 (9 [6–13] *vs* 57 [27–209] pg ml^{-1}; $P<0.05$). Concentrations of IL-8 were lower in group 1 than in group 2 at T3 (0 [0–9] *vs* 13 [7–20] pg ml^{-1}; $P<0.05$), T4 (6 [0–12] *vs* 46 [17–268] pg ml^{-1}; $P<0.05$), T5 (15 [7–35] *vs* 360 [128–1618] pg ml^{-1}; $P<0.05$) and T6 (5 [0–9] *vs* 11 [7–30] pg ml^{-1}; $P<0.05$). Serum concentrations of IL-6 (Fig. 3) increased in both groups above the pre-induction values starting from T3 and peaked at T5 ($P<0.05$) but the concentrations were significantly lower in group 1 than in group 2 at T4 (14 [10–33] *vs* 99 [35–229] pg ml^{-1}; $P<0.05$), T5 (108 [60–209] *vs* 1000 [354–1000] pg ml^{-1}; $P<0.05$) and T6 (31 [19–45] *vs* 90 [48–147] pg ml^{-1}; $P<0.05$).

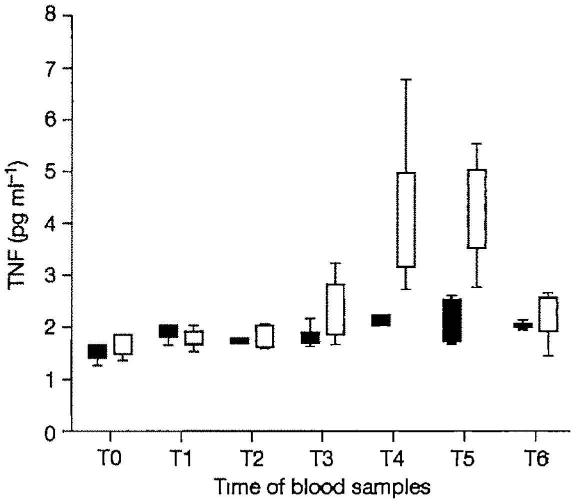

Fig 1 Serum tissue necrosis factor (TNF) concentrations expressed as median, quartiles, and extremes for logarithm transformation. T0, before induction of anaesthesia; T1, immediately before skin incision, T2, immediately before cardiopulmonary bypass; T3, after aorta-declamping; T4, end of CBP, T5, 2 h after skin closure, T6, 24 h after skin closure. Dark bars show group 1 and light bars show group 2

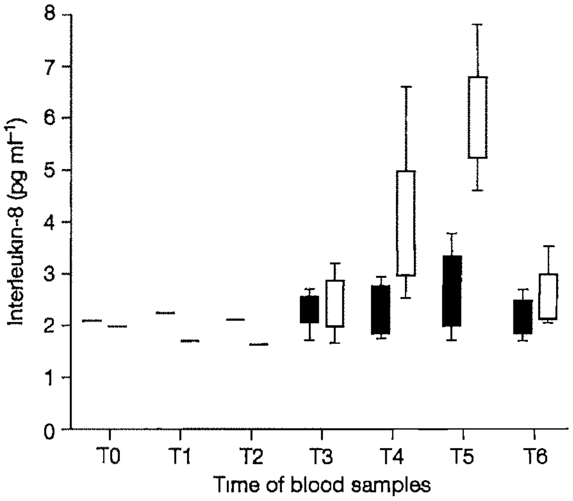

Fig 2 Serum IL-8 concentrations, expressed as median, quartiles, and extremes for logarithm transformation Definitions of time points are given in Fig 1. Dark bars show group 1 and light bars show group 2

In comparison with the pre-induction value, concentrations of IL-10 (Fig. 4) increased in group 1 from T2 to T6 ($P<0.05$), with a maximum at T4; in group 2 concentrations of IL-10 increased from T3 to T6 ($P<0.05$) and were greatest at T5. The concentrations of IL-10 were significantly greater in group 1 than in group 2 at T2 (13 [11–21] *vs* 0 [0–11] pg ml^{-1}; $P<0.05$), T3 (123 [46–275] *vs* 27 [15–65] pg ml^{-1}; $P<0.05$) and T4 (274 [136–446] *vs* 57 [38–222] pg ml^{-1}; $P<0.05$).

Serum concentrations of IL-4 (Fig. 5) did not change significantly in group 1 whereas they decreased in group 2 compared with the pre-induction concentrations from T1 to

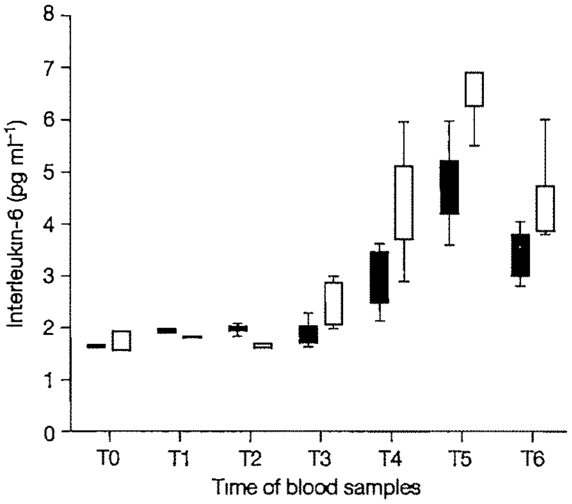

Fig 3 Serum IL-6 concentrations, expressed as median, quartiles, and extremes for logarithm transformation Definitions of time points are given in Fig 1 Dark bars show group 1 and light bars show group 2

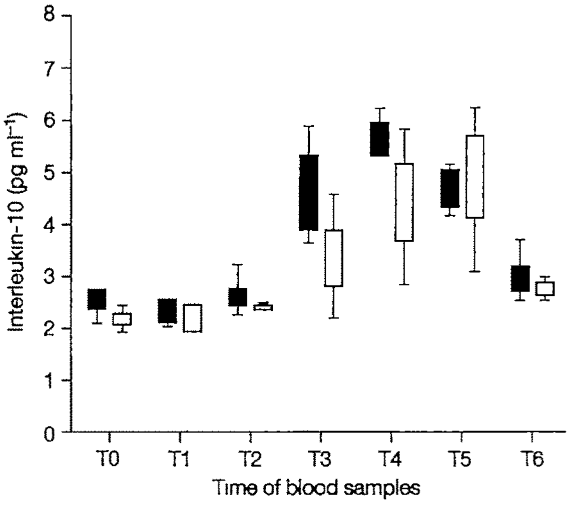

Fig 4 Serum IL-10 concentrations, expressed as median, quartiles, and extremes for logarithm transformation Definitions of time points are given in Fig 1 Dark bars show group 1 and light bars show group 2

T5 (P<0.05). The ratio of IL-10 to TNF-α was greater in group 1 than in group 2 at T2 (3 [1] *vs* 1 [1]; P<0.05), T3 (28 [21] *vs* 4 [4]; P<0.01), T4 (33 [15] *vs* 3 [5]; P<0.01) and T5 (2 [2] *vs* 12 [5]; P<0.01). The follow-up of patients is shown in Table 3. The maximum heart rate and respiratory rate and the maximum and minimum temperatures were significantly greater in group 2 than in group 1. The length of stay in the ICU was significantly shorter in group 1 than in group 2 (Fig. 6). The maximum arterial pressure and cardiac index seemed less in group 2. There were no major complications or mortality.

Discussion

Our data show that dexamethasone shifts the circulating cytokine balance towards the anti-inflammatory direction. Dexamethasone abolished the TNF-α and IL-8 responses, reduced the IL-6 response, and exaggerated the IL-10 response. TNF-α is an important mediator involved in the pathogenesis of myocardial ischaemia-reperfusion injury.[12] TNF-α reduces myocardial contractility and ejection fraction, and causes hypotension, decreased systemic vascular resistance and biventricular dilatation.[3 4] These effects can explain the lower cardiac index in the control group in our study, although this was not statistically significant.

IL-8 affects ischaemia-reperfusion injury through an effect on neutrophil activation and adherence to the vascular endothelium.[13] Treatment with anti-IL-8 antibodies prevents lung ischaemia-reperfusion injury in rabbits.[14] This could explain the higher mean pulmonary artery pressure we noticed in the control group, who had high IL-8 concentrations.

Our results confirm those of others[10 11] that corticosteroid administration inhibits but does not abolish the IL-6 response. This is because the production of IL-6 is affected by the degree of surgical trauma and tissue damage, as well as the effect of CPB.[15] Hennein and colleagues suggested that IL-6 may be a sensitive indicator of myocardial damage, and reported an association between the IL-6 response and cardiac morbidity.[3] Cruickshanks and colleagues reported that high concentrations of IL-6 had a negative inotropic effect, possibly by impairing entry of calcium into myocardial cells.[16]

IL-10 has been described as a cytokine synthesis inhibitory factor, and the most potent inhibitor of IL-8.[17] This may explain the abolished TNF-α and IL-8 response and the weak IL-6 response in the dexamethasone-treated group, in whom the IL-10 response was greater.

IL-4 inhibits the differentiation and action of Th 1 cytokines. It can antagonize these inflammatory responses,

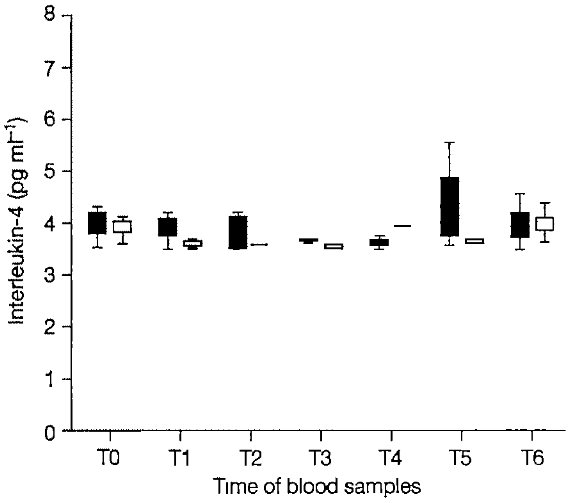

Fig 5 Serum IL-4 concentrations, expressed as median, quartiles, and extremes for logarithm transformation Definitions of time points are given in Fig. 1. Dark bars show group 1 and light bars show group 2

Table 3 Postoperative characteristics of patient groups Data are mean (SD); * statistically significant difference between the groups

	Group 1 (n=9)	Group 2 (n=8)	P value
Minimum mean arterial pressure (mm Hg)	60 (29)	60 (7)	0.54
Maximum mean arterial pressure (mm Hg)	112 (13)	97 (16)	0.05
Minimum heart rate (beats min^{-1})	73 (17)	75 (12)	0.83
Maximum heart rate (beats min^{-1})*	101 (11)	119 (19)	0.03
Minimum cardiac index	2.9 (0.7)	2.5 (0.4)	0.17
Maximum cardiac index	4.9 (0.9)	3.7 (0.8)	0.05
Minimum mean pulmonary artery pressure (mm Hg)*	10 (1)	15 (3)	0.01
Maximum mean pulmonary artery pressure (mm Hg)	23 (3)	27 (5)	0.11
Minimum respiratory rate (bpm)	10 (1)	10 (1)	0.71
Maximum respiratory rate (bpm)*	13 (3)	18 (3)	0.01
Minimum temperature (°C)*	34 (0.4)	36 (0.7)	0.00
Maximum temperature (°C)*	37 (0.7)	38 (0.5)	0.00
Time to tracheal extubation (h)	11 (2)	13 (3)	0.15
Length of stay in ICU (h)*	24 (8)	52 (32)	0.01
Need for inotropic support (number of patients)	2	3	0.62

which can cause excessive tissue destruction.[18] In our study IL-4 decreased in the control group before skin incision. Thereafter, the pro-inflammatory cytokines increased after aortic declamping. Thus, low concentrations of IL-4 may be another reason for the greater pro-inflammatory cytokine response in this group.

The effect of steroids on the cytokine balance during cardiac surgery has been previously studied by Kawamura and colleagues.[19] They gave methylprednisolone 30 μg kg^{-1} before CPB and declamping, and investigated IL-6, IL-8, IL-10 and IL1ra, whereas we investigated TNF-α, IL-6, IL-8, IL-4 and IL-10. In their patients, methylprednisolone did not abolish the IL-8 response as the dexamethasone did in our patients, but the response was inhibited. They found a balanced pro-inflammatory and anti-inflammatory response. In our study, the balance was shifted towards the anti-inflammatory responses. These differences may be the result of the different times of steroid injection or the different doses of steroid. The finding that the pre-induction dose of dexamethasone in our patients was associated with unbalanced cytokine response may be relevant, because wound healing and resistance to infection may depend on this balance. A perioperative pro-inflammatory cytokine response, held in balance by a concomitant anti-inflammatory response could be important.[20]

The mechanisms involved are far from clear. In non-cardiac-surgery patients, immunosupression has often been associated with exaggerated production of IL-10 and a high ratio of IL-10 to TNF-α.[21 22] Although the dexamethasone group in our study had a high ratio of IL-10 to TNF-α, no patients had adverse events such as infectious complications or sepsis in the postoperative period. These patients were discharged earlier than those in the control group, which could suggest reduced morbidity in the dexamethasone group.

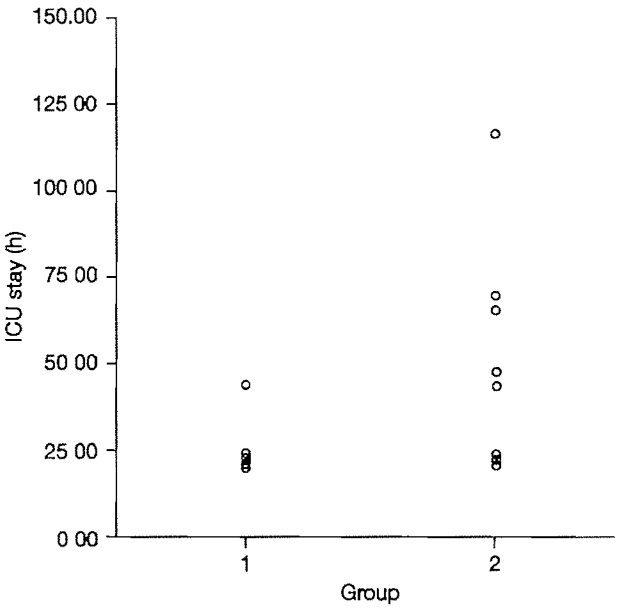

Fig 6 Scatter plot for the length of stay in the ICU.

In our study the clinical effects of dexamethasone in the postoperative period were shown by normothermia, lower heart rate and lower respiratory rate, which may indicate a smaller systemic inflammatory response.

Inhibition of TNF-α and IL-6 by dexamethasone might explain the greater cardiac index and arterial blood pressure in group 1. Reduced temperature in the immediate post-operative period can be advantageous in cardiac surgery patients, because oxygen consumption is directly related to temperature.[23] However, Chaney and colleagues showed that methylprednisolone had no clinical benefits in patients undergoing elective CABG and possibly hindered early postoperative tracheal extubation.[24] This contrasts with our finding that the dexamethasone-treated patients were extubated earlier than the control patients (albeit statistically insignificant).

The small size of our study is not sufficient to assess clinical outcomes. The main purpose of the present study was to investigate the effect of steroid on the cytokine balance. Our results can only partly confirm the improvements of clinical outcome found in previous investigations,[8 19 25 26] which may explain the shorter stay in the ICU in our study and in that of Jansen and colleagues.[8] We conclude that dexamethasone before cardiac surgery shifts the circulating cytokine profile towards the anti-inflammatory responses and may improve the postoperative course by inhibition of the systemic inflammatory response. Future studies should consider the correlation between circulating cytokines and clinical course.

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Effect of sevoflurane/nitrous oxide *versus* propofol anaesthesia on somatosensory evoked potential monitoring of the spinal cord during surgery to correct scoliosis

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Background. Use of intraoperative somatosensory evoked potential (SSEP) monitoring is helpful in spinal corrective surgery but may be affected by anaesthetic drugs. An anaesthetic technique that has less effect on SSEP or allows faster recovery is an advantage. We compared the effects on SSEP and the clinical recovery profiles of sevoflurane/nitrous oxide and propofol anaesthesia during surgery to correct scoliosis.

Methods. Twenty adolescent patients were randomized into two groups of 10. One group received sevoflurane–nitrous oxide anaesthesia and the other received propofol i.v. anaesthesia. An alfentanil infusion was used for analgesia in both groups.

Results. Changes in anaesthetic concentration produced little effect on the latency of SSEP, but the effect on the variability of SSEP amplitude was significant ($P<0.05$). Sevoflurane produced a faster decrease in SSEP and a faster recovery than propofol ($P<0.05$). On emergence, patients who received sevoflurane tended to have shorter recovery times to eye opening (mean 5.1 *vs* 20.6 min, $P=0.09$) and toe movement (mean 7.9 *vs* 15.7 min, $P=0.22$). Those who had received sevoflurane were significantly more lucid and cooperative in recovery.

Conclusions. Sevoflurane produces a faster decrease and recovery of SSEP amplitude as well as a better conscious state on emergence than propofol.

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Keywords: anaesthetics volatile, sevoflurane; anaesthetics i.v., propofol; monitoring, somatosensory evoked potential; surgery, spinal

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The use of continuous or intermittent intraoperative electrophysiological spinal cord monitoring provides information concerning the neurological structures at risk during spinal corrective surgery. The Scoliosis Research Society has published a position statement concerning the use of intraoperative monitoring during spinal surgery, and made recommendations concerning standard monitoring techniques.[1] Somatosensory evoked potentials (SSEP) remain the most widely used monitoring method for spinal surgery.[2] This is largely related to familiarity with the method, comparative ease of application and its proven sensitivity to an array of surgical variables. SSEPs are signal-averaged data, elicited by stimulating a peripheral nerve and recording the response at points along the afferent pathway and across the somatosensory cortex. They are small-amplitude responses that are not identifiable with a single stimulus. Instrumentation used to record these data amplifies and filters the signal over multiple trials to produce a response that can be measured and duplicated. Typically, 300–500 samples are averaged to create one SSEP response and take about 60 s to obtain. They are, therefore, a measure of neural transmission in afferent spinal cord pathways. However, anaesthetic drugs can affect SSEP findings. Sevoflurane can increase the latency and

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decrease the amplitude of SSEP in a dose-dependent fashion.[3] Propofol–sufentanil total i.v. anaesthesia has also been shown to influence SSEP monitoring.[4] Anaesthesia may, therefore, affect the interpretation of an unfavourable intraoperative SSEP and a drug that has less effect on SSEP or allows a faster recovery of SSEP after readjustment of anaesthetic dose is advantageous.

Although electrophysiological monitoring is an important breakthrough, the Stagnara 'wake-up' test has largely remained the gold standard for assessment of neurological status during spinal surgery.[5] The wake-up test may be required in circumstances in which SSEP signals are undetectable or abnormal. However, timely completion of an intraoperative wake-up test can be difficult and the critical time window for reversal of a deficit can be lost while waiting for a patient to recover consciousness. Should a wake-up test become necessary, an anaesthetic technique that facilitates more rapid, lucid recovery can be helpful. The low blood–gas partition coefficient of sevoflurane or the short, context-sensitive half-time of propofol may confer advantages in such scenarios. Previous studies have shown that recovery after sevoflurane is faster than after isoflurane,[6] halothane[7] and propofol.[8–11]

The aims of this study were (i) to compare inhalational sevoflurane/nitrous oxide anaesthesia with total i.v. anaesthesia (TIVA) with propofol for their abilities to preserve SSEP monitoring signals during corrective scoliosis surgery, and (ii) to compare the wake up profiles of these techniques.

Patients and methods

Approval for this prospective, randomized study was obtained from the research ethics committee of the University of Hong Kong. Twenty patients with adolescent idiopathic scoliosis undergoing spinal fusion and instrumentation at the Duchess of Kent Children's Hospital were enrolled. All patients were ASA class II. Patients with neurological deficit, congenital musculoskeletal disease, learning difficulties or cerebral palsy were excluded. Informed consent was obtained from all patients and their parents.

Patients were allocated randomly into two groups of 10. Randomization was done by drawing lots from an envelope containing 20 small pieces of paper, 10 marked 'S' and 10 marked 'P'. Group 1 (lots marked S) received sevoflurane/nitrous oxide inhalational anaesthesia and Group 2 (lots marked P) received propofol TIVA. EMLA cream (AstraZeneca LP, Wilmington, USA) was applied to facilitate painless insertion of an i.v. cannula and patients were not premedicated. Anaesthesia was induced with alfentanil 40 μg kg^{-1} and propofol 2–3 mg kg^{-1}. Atracurium 0.5 mg kg^{-1} was given for muscle relaxation and was followed by tracheal intubation and intermittent positive pressure ventilation. Maintenance of anaesthesia in the sevoflurane group was provided with a mixture of 65% nitrous oxide and 35% oxygen with 0–3% sevoflurane [<1.5 minimum alveolar concentration (MAC)], titrated to clinical requirement. Anaesthesia was maintained in Group 2 by target-controlled infusion (TCI) of propofol (Diprifusor; AstraZeneca) at a plasma concentration of 2–5 μg ml^{-1}, titrated to clinical requirement while the patient was ventilated with 35% oxygen in air. Muscle relaxation was maintained with atracurium 0.3–0.5 mg kg^{-1} h^{-1}. Intraoperative analgesia was provided by an alfentanil infusion of 0.4–1.0 μg kg^{-1} min^{-1}, with intermittent boluses of 150–500 μg as required. No other opioid was given until after completion of the study. The infusion of atracurium was discontinued towards the end of surgery and reversed using neostigmine 40 μg kg^{-1} and atropine 20 μg kg^{-1}. Patients were kept normothermic with forced air warmers.

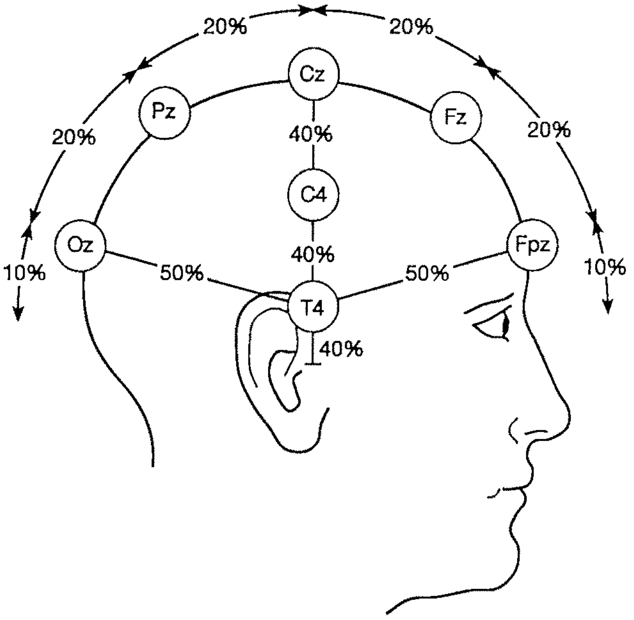

Fig 1 The 10–20 international system of EEG electrode placement. Cz′ is located 2 cm posterior to Cz.[12]

Intraoperative monitoring included intraradial invasive arterial blood pressure, rectal temperature, capnography, end-tidal sevoflurane concentration, pulse oximetry, central venous pressure, urine output and peripheral nerve stimulation. Arterial blood gases and haematocrit were checked intermittently. SSEP signals were collected over Cz′ (2 cm posterior to Cz; 10–20 international system of EEG electrode placement) and Cv (over the cervical spinal process of C2) *vs* the Fz of the 10–20 system (Fig. 1).[12] To elicit SSEPs, a pair of stimulating electrodes was applied over the posterior tibial nerve behind the medial malleolus. The stimulation current used ranged from 10 to 30 mA and was kept constant once selected for a particular patient. The normal current density was adjusted to produce a small movement of the toes. Single-pulse stimulation with a frequency between 5.1 and 5.7 Hz and duration of 200 μs was applied. An intraoperative spinal cord monitoring

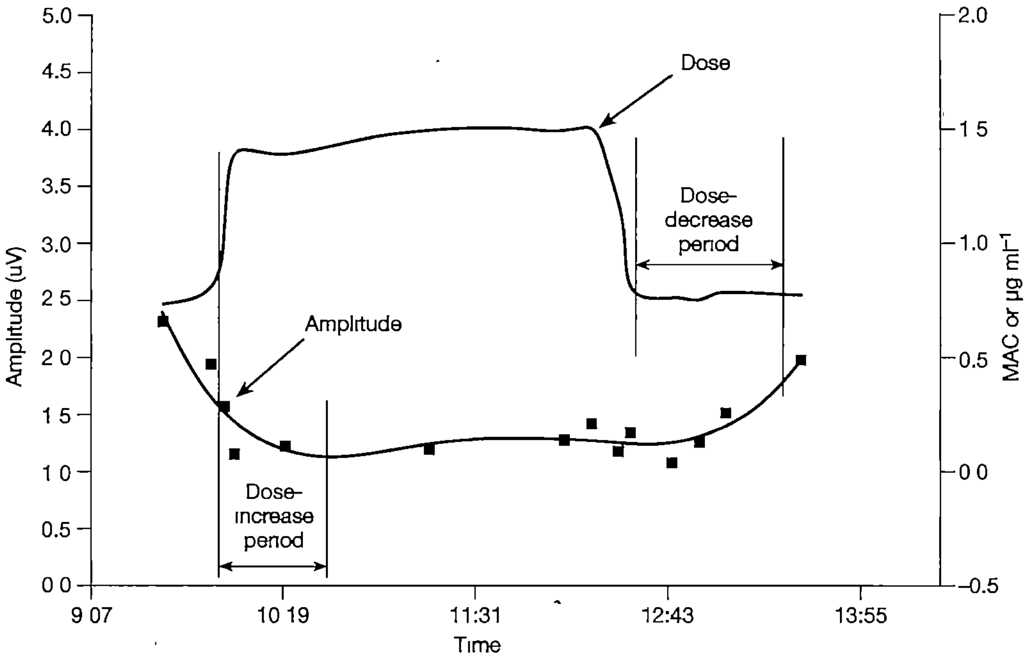

Fig 2 An example of the changes in SSEP amplitude and dose plotted on a scatter chart corresponding to time. The upper curve represents the dose changes during surgery Units are MAC in the sevoflurane group and μg ml^{-1} in the propofol group The lower curve shows contemporaneous changes in SSEP amplitude (μV) The dose-increase period was measured from the point when the dose was increased by 30% from the baseline to the time when the SSEP amplitude reached a plateau. The dose-decrease period was measured from the point when the dose returned to baseline to the point when SSEP amplitude had increased to 70% of its baseline value.

system (Viking IV; Nicolet Biomedical, Madison, WI, USA) was employed to record the responses with a 20–3000 Hz bandpass filter. Continuous 100 times averaging was used. The initial negative and positive waves were identified in the SSEP tracings so that the latency and the peak-to-peak amplitude could be measured. The intensity changes related to anaesthesia were also noted during surgery. The mean values and standard deviations of these variables were calculated for each patient. The within-patient variability was calculated from the ratio of the standard deviation to the mean [(SD/mean)×100%].

The results for the two groups were analysed statistically with the paired Student's *t*-test, with the level of significance set at $P<0.05$. Statistical analysis was performed using SPSS 8.0 for PC Windows (SPSS, Chicago, IL, USA). The changes in SSEP amplitude in response to changes in anaesthetic dose were analysed with a scatter chart corresponding to time, where the trend lines of SSEP amplitude and anaesthetic dose changes were plotted with a best-fit polynomial function. The delay period was measured between the inflection points of the trend line of anaesthetic dose and SSEP variables. The delay periods were defined as two types of change in anaesthetic dose. One was the dose-increase period, i.e. decrease in SSEP amplitude with increasing anaesthetic dose. The dose-increase period was measured from the time the dose was increased by 30% from the baseline to the time that the SSEP amplitude reached a plateau. The other was the 'dose-decrease' period, measured from the time that the dose was decreased back to baseline to the time that the SSEP amplitude increased to 70% of its baseline value. Figure 2 illustrates an example of the measurement of the dose-increase and dose-decrease periods in a patient undergoing sevoflurane anaesthesia; the dose changes are represented by MAC. If the patient received propofol anaesthesia, similar measurements were made on the plot of the trend line for dose change, the measurement unit being μg ml^{-1}.

Anaesthetic agents were stopped when the patient had been turned to the supine position after completion of surgery. Recovery was assessed with a simulated wake-up test. The patients were asked to open their eyes and move their toes and the time interval from cessation of anaesthesia was recorded. A behavioural score was determined at this point. As the physicians could not be blinded to the anaesthesia technique, it was necessary to provide a simple classification of the level of consciousness in order to decrease observer bias: 1=calm/cooperative/good; 2=confused/restless/disorientated; 3=drowsy/unable to obey commands.

Results

There were 10 patients in each group. All patients were female and Chinese. There was no significant difference between the groups with respect to age and weight. Table 1 shows the within-patient variability of SSEP variables related to the changes of doses of the different anaesthetic agents. Changing the anaesthetic dose produced little effect

Table 1 Within-patient variability of SSEP latency and amplitude in relation to changes in doses of sevoflurane and propofol. Values are mean percentage (SD). *$P<0.05$ compared with SSEP Cv amplitude (*t*-test)

	Dose variation	SSEP Cz′		SSEP Cv	
		Latency	Amplitude*	Latency	Amplitude
Propofol	23.7 (11.4)	2.2 (1.0)	18.0 (8.2)	1.9 (0.9)	16.3 (3.5)
Sevoflurane	34.4 (13.4)	3.5 (1.8)	34.9 (11.7)	2.6 (2.0)	16.4 (7.0)

Table 2 Anaesthetic effects on delay periods and the interval in minutes from cessation of anaesthetic to toe movement and eye opening. Values are mean (SD)

	Sevoflurane	Propofol	*P*
Dose-increase period	9.0 (1.7)	13.5 (5.8)	<0.001
Dose-decrease period	16.1 (3.0)	35.0 (11.5)	<0.001
Toe movement	7.9 (6.5)	15.7 (17.9)	0.22
Eye opening	5.1 (6.7)	20.6 (25.8)	0.09

Table 3 Pearson correlation coefficient (C) between duration of anaesthesia, total dose of alfentanil and eye opening and toe movement

	Toe movement	Eye opening
Duration of anaesthesia	$C=-0.003$ ($P=0.99$)	$C=-0.03$ ($P=0.89$)
Alfentanil	$C=0.17$ ($P=0.47$)	$C=0.14$ ($P=0.55$)

Table 4 Contingency table showing numbers of patients with different behavioural scores on emergence ($P=0.03$, Fisher's exact test)

Score	Sevoflurane	Propofol
1	9	4
2	0	5
3	1	1

on the latency of SSEP. The effect on the variability of Cz′ SSEP amplitude was statistically significant ($P<0.05$) compared with Cv SSEP amplitude, suggesting that Cv SSEP is more resistant to the effects of anaesthesia. There was no difference between the two anaesthetic techniques in this regard.

The dose-increase and dose-decrease delay periods were both shorter in the sevoflurane group ($P<0.05$, Table 2), indicating a faster decrease in SSEP and faster recovery than for propofol. The recovery times are also shown in Table 2. There was no correlation between duration of anaesthesia or total dose of alfentanil and time to toe movement or eye opening (Table 3). A contingency table was constructed to compare the behavioural scores on emergence between the two groups (Table 4). Patients in the sevoflurane group were significantly more lucid and cooperative.

Discussion

Spinal cord monitoring with SSEP has become a routine technique for detecting cord injury during spinal surgery, allowing early intervention to avoid permanent impairment. Its use has been found to correlate with neurosurgical outcome [13–15]. The effects of anaesthetic drugs on SSEP are, therefore, an important consideration. Our study shows that propofol and sevoflurane/nitrous oxide affect the amplitude of SSEP to a similar extent, assuming that the depth of anaesthesia is comparable in the two groups. Such a comparison, however, is difficult as it is not possible to measure the actual plasma concentration of propofol in real time (unlike end-tidal sevoflurane concentration) and, therefore, to make a direct comparison between sevoflurane MAC and the median effective concentration of propofol (EC_{50}). The bias and accuracy of the TCI system used has, however, been shown to be satisfactory,[16] [17] and clinical signs of anaesthetic depth were the same in both groups. Processed EEG modalities, such as the bispectral index (BIS) and the middle latency auditory evoked response (AEP), can be helpful in monitoring anaesthetic depth but neither has the sensitivity nor specificity to allow the clinician to draw conclusions about the depth of anaesthesia in individual patients. Furthermore, the values seen at similar clinical levels of anaesthesia vary according to the anaesthetic drug used.[18] However, the possibility that sevoflurane has a lesser effect on SSEP because of differences in the depth of anaesthesia cannot be discounted.

A sevoflurane concentration up to 1.0 MAC was still compatible with SSEP recording.[3] Other studies have found that propofol/alfentanil TIVA provides a better signal-to-noise ratio than enflurane or isoflurane anaesthesia, thereby allowing more frequent and reliable intraoperative SSEP recordings.[19] The TCI plasma propofol concentration that can preserve SSEP signals adequately is still to be determined. Our results also show that there is a significant change in SSEP Cz′ amplitude in response to changes in anaesthetic concentration when compared with SSEP Cv amplitude. This may reflect the cerebral effect of anaesthetic drugs rather than their effect on the spinal cord

Sometimes a higher concentration of anaesthetic may be required during surgical manipulation and a drug that allows faster recovery of SSEP after readjustment therefore permits more accurate interpretation of the data. In this regard, we found that sevoflurane had significantly shorter dose-increase and dose-decrease periods than propofol. Also, the smaller standard deviation suggests that the recovery time required is more predictable than that with propofol. In interpreting SSEP, however, it is important to realize that false negative results may occur because monitoring is pathway-specific and an injury not involving the pathway may not be detected. Failure to monitor both latency and amplitude or use of an insufficient number of recording electrodes can be responsible for false negative responses.[20] Also, patients with preoperative deficits may not have detectable SSEPs. More and colleagues reported six patients in a series of 158 who had no detectable potentials before anaesthesia.[21] False positive SSEP results may also occur as a result of changes in anaesthetic dose or technical problems, although the consequences are less serious. A large multicentre study of SSEPs for spinal cord monitoring found a sensitivity of 92%, specificity 98.9%, positive predictive value 42% and negative predictive value 99.93%.[22] Changes in SSEP may also be produced by physiological factors such as severe hypotension, hypoxia, hyperthermia and a large decrease in haematocrit (to less than 15%).[23] These did not occur in any of the patients in our study.

As well as a faster recovery time, our data from the behavioural scores showed that sevoflurane produces a better conscious state on emergence. As both groups were homogeneous with respect to age, sex, body weight, ethnicity and surgery, we can assume that this is related to the anaesthetic technique. Although there was some variation in the duration of anaesthesia and individual consumption of alfentanil, there was no correlation between the duration of anaesthesia or total dose of alfentanil per unit body weight and the recovery indices, i.e. times from cessation of anaesthesia to toe movement and eye opening. This is interesting, considering recent reports of restlessness in paediatric patients recovering from sevoflurane anaesthesia.[24] [25] A calm and cooperative patient is obviously preferable after spine stabilization surgery and in the event of a wake-up test being required.

Sevoflurane has been associated with more nausea and vomiting than propofol.[11] In our study, two patients in the sevoflurane group developed postoperative nausea and vomiting, but none in the propofol group did so before commencement of patient-controlled anaesthesia with morphine. Although propofol appears to have intrinsic anti-emetic properties, the number of patients in this study was too small to demonstrate this. One patient receiving sevoflurane had involuntary movement on wakening, but this was transient with no clinical consequence.

In conclusion, this study showed that both sevoflurane and propofol produced a significant change in SSEP amplitude but sevoflurane produced this change more quickly and with faster recovery than propofol. Patients receiving sevoflurane also had a faster, more predictable recovery from anaesthesia and a calmer, more cooperative state on emergence.

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Malignant hyperthermia associated with exercise-induced rhabdomyolysis or congenital abnormalities and a novel *RYR1* mutation in New Zealand and Australian pedigrees

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Malignant hyperthermia (MH) is rarely associated with specific myopathies or musculoskeletal abnormalities. Three clinical investigations of MH associated with either non-specific myopathies or congenital disorders in three separate families are presented. Two of these cases also show evidence of exercise-induced rhabdomyolysis. In each case MH susceptibility was confirmed by *in vitro* contracture testing of quadriceps muscle. DNA sequence analysis of each kindred revealed the presence of a common novel mutation that results in an arginine401–cysteine substitution in the skeletal muscle ryanodine receptor gene (*RYR1*). Haplotype analysis using chromosome 19q markers indicated that the three families are likely to be unrelated, providing confirmation that the MH/central core disease region 1 of *RYR1* is a mutation hot spot.

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Malignant hyperthermia (MH) is a pharmacogenetic disorder that predisposes to a potentially fatal hypermetabolic reaction to inhalational anaesthetics and depolarizing neuromuscular blocking agents.[1] An association with MH has been firmly established for three rare myopathies: central core disease (CCD), Evans myopathy and King–Denborough syndrome.[2 3] These conditions predispose to a drug-induced increase in myoplasmic calcium, which leads to hyperthermia, hypoxia and acidosis.[4 5] The association between MH and other myopathies is less clear,[6 7] with inconsistencies between the results of *in vitro* contracture testing (IVCT) and reactions under anaesthesia. In addition, MH-like symptoms unrelated to anaesthesia have been associated with strenuous exercise, excitement or environmental heat.[8–13] More recently, the connection between MH and exercise has been substantiated by the demonstration of both positive IVCT and the presence of ryanodine receptor (RYR) mutations in patients with a history of exercise-induced rhabdomyolysis (EIR).[14 15] Molecular genetic studies have mapped the primary MH-susceptibility locus to the *RYR1* gene on human chromosome 19q 13.1,[16 17] where 28 missense mutations have been

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identified to date.[18–23] The majority of *RYR1* mutations appear to be clustered between amino acid residues 35 and 614 (MH/CCD region 1) and amino acid residues 2163 and 2458 (MH/CCD region 2) and are predicted to reside in the myoplasmic foot region of the protein.[24,25] A third region for mutations (MH/CCD region 3) has recently been identified and is predicted to be in the luminal/transmembrane domain of the protein.[19,22,26,27] Here we report the clinical and molecular genetic analysis of three unrelated families with non-specific myopathies associated with EIR or congenital musculoskeletal abnormalites which indicate that the same single missense mutation in MH/CCD region 1 co-segregates with MH susceptibility (MHS) in each family.

Methods

Patients and samples

Blood and tissue samples were obtained following informed consent from members of three families participating in this study. Ethical approval was obtained from the Manawatu-Whanganui and Massey University Ethics Committees or from the Human Rights Committee, Research Administration Unit, The University of Western Australia.

In vitro *contracture testing*

IVCT of muscle biopsies was carried out according to the European MH group protocol.[28] IVCT is based on contracture tensions induced in muscle *in vitro* by caffeine and halothane. A diagnosis of MHS is made when contractures of 0.2 g or greater are induced individually by a halothane concentration of 2% or less and a caffeine concentration of 2 mM or less. A diagnosis of MH equivocal (MHE) is made when contractures of 0.2 g or greater are induced with either halothane or caffeine, but not both, at the above concentrations.

Muscle histology

Histological examination using both light microscopy and electron microscopy was performed in the Western Australian laboratory on samples from all patients tested for susceptibility to MH. Light microscopy only was carried out in the New Zealand laboratory. Ten-micron sections from frozen muscle specimens were stained or reacted for hematoxylin and eosin, modified Gomori trichrome, NADH-tetrazolium reductase, ATPase, acid phosphatase, periodic acid–Schiff, and oil red O.[29]

Mutation screening by RT-PCR and DNA sequencing

Total RNA was extracted from 30–100 mg frozen skeletal muscle tissue using Trizol™ RNA extraction reagent (Invitrogen, Groningen, The Netherlands). First strand synthesis was carried out using the Superscript reverse transcriptase (RT) pre-amplification system (Invitrogen) with 4 µg total RNA and either 50 ng random hexamers or 500 ng oligo(dT) in a 20 µl volume. Hot-start polymerase chain reaction (PCR) was performed using 1 µl of a 20-fold dilution of the first strand cDNA reaction in 50 µl reactions with 0.32 µM of each primer, 0.3 mM dNTPs, 1.5 mM $MgCl_2$ and 1.5 U *Taq* polymerase (Invitrogen). MH/CCD region 1 was amplified in three overlapping 816 bp, 824 bp, and 578 bp fragments using the following primer pairs: CAGGAGGACGCAACAGGAGAG/GTTGTATAGGCCATTGGTGCT; TCCAAGGAGAAGCTGGATGTGG/TGCTTGTCCAGGAGGGAGATG and CTCTCCATGGTCCTGAATTGCATAGAC/AGTCACCTCGTCCACCATCAC, respectively. MH/CCD region 2 was amplified in one 1101 bp fragment using the CAGTACGACGGGCTGGGTGAG/GGATGCTGACATCTTTGGCT primer pair. MH/CCD region 3 was amplified in one 630 bp region using the GAACCCGCCCTGCGCTGTCTG/GTAGACGACCACCGCCAGAAG primer pair. PCR products were purified using the Concert™ rapid PCR product purification kit (Invitrogen) and then screened for the presence of mutations by automated DNA sequencing using an ABI 377-36 or 373 with Big-Dye terminator chemistry (Applied Biosystems, New Zealand). Exon 12 of *RYR1* was amplified from genomic DNA using primers 1143F and 1213R,[5] purified using the Concert™ rapid PCR product purification kit (Invitrogen) and sequenced from the forward primer using an ABI 377-36 or 373 with Big-Dye terminator chemistry (Applied Biosystems).

SSCP analysis and allele-specific PCR

Genomic DNA was isolated using the Wizard DNA extraction kit (Promega Corporation, Madison, USA) according to the manufacturer's instructions. Exon 12 of *RYR1* was amplified as above and screened for the presence of the C1201T mutation by single-stranded conformation polymorphism (SSCP) analysis using 12% 29:1 polyacrylamide gel electrophoresis. Alternatively, an allele-specific probe (CAGGCCGCCCGCATGAT) labelled with fluorescein together with an anchor probe (CAGCACCAATGGCCTATACAACCAGTTCATCAAGTGA) labelled with LC-red 640 was used to detect the presence of the C1201T mutation by real-time amplification of genomic DNA using a Light Cycler (Roche Diagnostics, NZ Ltd, Auckland, New Zealand).[30,31] The sequences of the flanking primers were as follows: CTCTGTCTCCCCACTCCTA (forward) and GGCAACAGAGGTAGAGATGAA (reverse). The oligonucleotide primers and probes were designed using the software MeltCalc (http://www.meltcalc.de). The following thermocycling protocol was used for amplification: denaturation at 95°C for 120 s, followed by 45 cycles of: 95°C for 0 s, 55°C for 10 s, 72°C for 11 s, with a temperature transition rate of 20°C s^{-1} and

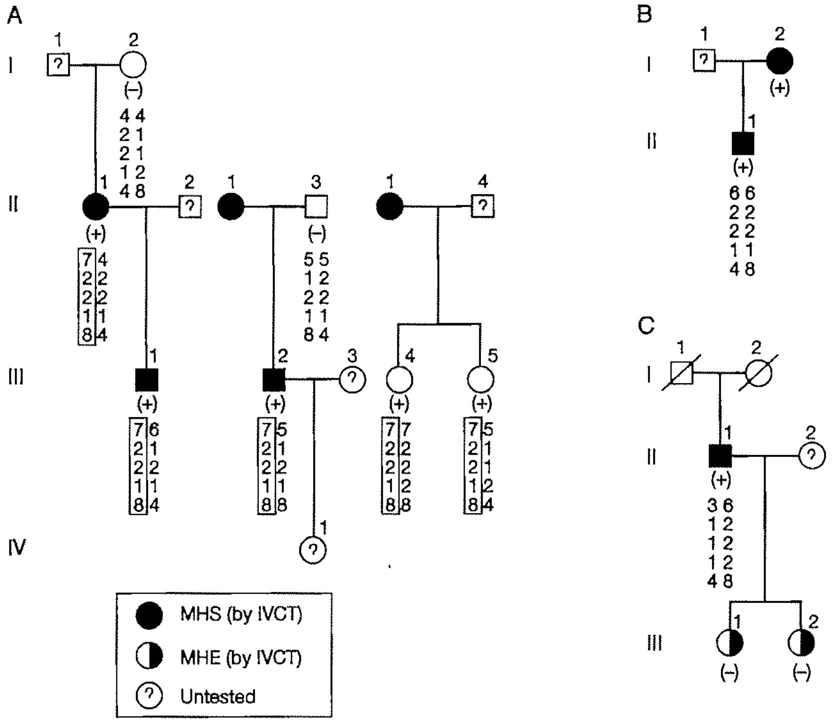

Fig 1 Pedigree diagrams (A) New Zealand Maori kindred with congenital abnormalities. The proband's mother (II-1) has had three partners (B and C) Australian kindreds with non-specific muscle myopathies The chromosome 19 haplotype (D19S220, Ile1151, Asp2729, Ser2862, D19S47) co-segregating with MH is shown boxed. The haplotypes are represented as alleles[32 33 35] (+) and (–) refer to presence or absence, respectively, of the C1201T mutation

data acquisition at the annealing step. The melting curve analysis was as follows: 95°C for 0 s, 45°C for 30 s, with a temperature transition rate of 20°C s^{-1}, followed by 75°C for 0 s at a temperature transition rate of 0.1°C s^{-1} with continuous data acquisition. For each step in the protocol the fluorescence display was F2/1. The melting temperatures of the wild-type and mutant alleles were 64.5°C and 57.5°C, respectively.

Haplotype analysis

Haplotype analysis was carried out using the D19S220[32 33] and D19S47[34] chromosome 19q microsatellite repeat markers that flank the *RYR1* locus. The forward primer of each pair was labelled with 6-FAM and the microsatellite regions were amplified independently using standard PCR reactions. The reactions were diluted 1:5 in distilled water, pooled, and analysed on an ABI 377-36 using Genescan software (Applied Biosystems). Allele identities and frequencies were as published. Three intragenic restriction fragment length polymorphism (RFLP) markers,[35] Ile1151 (*Taq* I), Asp2729 (*Fok* I) and Ser 2862 (*Cfo* I), were typed by restriction endonuclease digestion of the amplified polymorphic regions. By convention, alleles that lack the polymorphic restriction sites were denoted '1' and those with the polymorphic restriction endonuclease sites were denoted '2'.

SNAPshot™ mutation detection

A SNAPshot™ (Applied Biosystems) dideoxy primer extension method was used as a diagnostic test for the presence of the C1201T mutation according to the manufacturer's instructions. PCR products were amplified from genomic DNA using the exon 12 primers described above and purified using the Concert™ rapid PCR product purification kit (Life Technologies, Auckland, New Zealand). Five nanograms of PCR product were used in the primer extension reaction with the primer TGGT-GCTGTGGATCATGC and the reactions were analysed on an ABI 377-64 using Genescan software (Applied Biosystems).

Results

Clinical investigation

Family 1

The proband (III-1, Fig. 1A) was a 45 kg, 11-year-old male of Maori descent undergoing dental treatment under general anaesthesia. He had previously had uneventful anaesthesia at 9 years of age for a similar procedure. There was no known personal or family history of anaesthetic problems or any adverse reactions during or after exercise.

The patient was premedicated with oral midazolam 7.5 mg. Propofol 100 mg i.v. and suxamethonium 50 mg i.v. were used for induction and intubation. There was no masseter spasm at induction. Anaesthesia was maintained with halothane and spontaneous breathing. During the first 20 min the heart rate increased from 100 to 120 beats min^{-1} but this settled partially with fentanyl 40 μg. However, over the next 30 min the heart rate increased to 140 beats min^{-1} and the end tidal CO_2 (E'_{CO_2}) increased from 50 to 65 mm Hg towards the end of the procedure, about 55 min after induction. At insertion of a paracetamol suppository, it was noticed that the legs were stiff. An MH reaction, which had been considered earlier, was strongly suspected because of the muscle rigidity. Halothane was discontinued and 100% oxygen given from a cylinder by Laerdal bag. Axillary temperature was 37.5°C. Clothing was removed and the air conditioning was switched on, but no active cooling was undertaken. The temperature reached a maximum of 38.2°C and the E'_{CO_2} 70 mm Hg over the next 8 min, but the temperature had settled to 37.3°C 20 min later. Arterial blood gases showed pH 7.28, Pa_{CO_2} 50 mm Hg and base excess −2.0 mmol litre^{-1}. Serum potassium measured 4.0 mmol litre^{-1}. Initial creatine kinase (CK) was measured at 53 200 i.u. (normal range: 20–215 i.u.) 2 h after the reaction, and the urine was strongly positive for myoglobin 6 h after the reaction. CK peaked at 165 000 i.u. 1 day after the reaction. There were no further problems, although the patient complained of aching arms and legs for 24 h.

IVCT conducted 2 yr later recorded a contracture of 5.5 g with 2% halothane (normal value <0.2 g) and 2.7 g with 2 mM caffeine (normal value <0.2 g), indicative of a strong MHS response. Histology and histochemistry were reported as normal. IVCT carried out at a later date in both mother (II-1, Fig. 1A; 2% halothane 1.7 g, 2 mM caffeine 0.35 g) and one sibling (III-2, Fig. 1A; 2% halothane 2.8 g, 2 mM caffeine 1.9 g) were also indicative of MHS status.

The medical and anaesthetic histories of three siblings were also of interest. The older sibling (III-2, Fig. 1A) had undergone repair of harelip and cleft palate in infancy. However, anaesthetic records were unavailable. Two younger siblings (III-4 and III-5, Fig. 1A) had received multiple anaesthetics for clubfoot surgery. The history of MH was unknown for these anaesthetic procedures and both children had received trigger agents. Neither child has been biopsied because of age, but in one procedure the younger of the two (III-5, Fig. 1A) developed tachycardia, pyrexia towards the end of the operation and tachypnoea in recovery. The older of the two (III-4, Fig.1A) had similar findings, with increased E'_{CO_2}. In retrospect these may have been developing MH reactions.

Family 2

The proband (I-2, Fig. 1B) was referred for muscle biopsy because of a history of sporadically elevated CK levels (5212 and 203 i.u.) and intermittent muscle pain and muscle cramps, often precipitated by exercise. These episodes occurred several years apart but lasted for 2 weeks, with difficulty in walking because of muscle pain rather than weakness. She had no previous general anaesthetics and there were no anaesthetic records for other family members. IVCT was indicative of MHS status and demonstrated a static halothane threshold of 1% (maximum contraction of 1.8 g), a dynamic halothane threshold of 1% (maximum contraction of 1.3 g) and a caffeine threshold of 1.0 mM. Histology showed numerous basophilic fibres with prominent nuclei and non-specific necrosis, type 2 fibre predominance with type 1 grouping. Regeneration was in phase, suggesting recent specific muscle injury coinciding with the high CK (5212 i.u.) and her symptoms at referral. Electron microscopy showed a few atrophic fibres with a few areas of Z-band streaming. A neurological examination was normal. Her son (II-1, Fig. 1B), who routinely suffers from muscle cramps after playing sport, also tested MHS by IVCT, with a static halothane threshold of 1% (maximum contraction of 0.8 g), a dynamic halothane threshold of 0.5% (maximum contraction of 1.2 g) and a caffeine threshold of 1.5 mM. Histology and histochemistry were normal.

Family 3

The proband (II-1, Fig. 1C) was referred for muscle biopsy because of elevated serum enzymes after exercise in hot weather, and a history of muscle cramps. CK was recorded at 899 i.u.. He had previously undergone two general anaesthetics with no apparent problems. IVCT results were indicative of MHS status: static halothane threshold of 0.5% (maximum contraction of 1.4 g), a dynamic halothane threshold of 0.5% (maximum contraction of 2 g) and a caffeine threshold of 1.5 mM. Histology and histochemistry showed an increased variability in fibre size and an increased number of internal nuclei in 30% of 140 fibres. Two of his daughters (III-1 and III-2, Fig. 1C) tested MHE by IVCT with the following results. III-1: static halothane normal, dynamic halothane threshold at 0.5% (maximum contraction of 0.5 g) and caffeine normal; III-2: static halothane threshold of 2% (maximum contraction of 0.4 g), dynamic halothane threshold of 0.5% (maximum contraction of 0.5 g) and caffeine normal. A neurological examination showed no evidence of clinical signs that might indicate MH. One of the proband's daughters (III-1, Fig. 1C) had had four uneventful general anaesthetics and the muscle was morphologically unremarkable, with no evidence of myositis or other recognizable pathology. The other daughter (III-2, Fig. 1C) had no anaesthetic history, and normal skeletal muscle by histology. Electron microscopy showed some atrophic fibres indicative of non-specific atrophy.

RYR1 mutation screening

The *RYR1* gene contains 106 exons spanning 160 kb of DNA[36] but most MH-associated mutations are located within three hot-spot regions, designated MH/CCD regions 1, 2 and 3.[19] Each of these regions was amplified using RT-PCR from RNA prepared from muscle biopsy tissue from individual III-1 in family 1 (Fig. 1A) and sequenced in both directions. Two novel silent polymorphisms (cgc/t-R2403 and gcc/t-A2427) were detected and one missense C1201T mutation (in exon 12 of *RYR1*) that substitutes Arg401 for Cys. Exon 12 was amplified from genomic DNA from the proband's mother (II-1, family 1) and each of her offspring (III-2, III-4 and III-5), and sequenced. The C1201T mutation was identified in each of these individuals.

The C1201T mutation was also identified in individuals I-2 (Fig. 1B) and II-1 (Fig. 1C) after sequencing the majority of the *RYR1* cDNA as described previously.[19] The mutation was also identified in individual II-1 (Fig. 1B) by sequencing exon 12 amplified by PCR using primers 1143F and 1213R.[5] The C1201T mutation was not identified in the two MHE individuals (III-1 and III-2 from family 3; Fig. 1C).

As the C1201T transition does not alter any informative restriction sites, alternative methods were used to screen for the mutation in the normal population. A total of 200 unrelated DNA samples (400 chromosomes) were screened by SSCP analysis or allele-specific PCR using the Light Cycler by amplifying genomic DNA. The mutation was not detected in any normal chromosomes from unrelated control subjects of either Maori or Caucasian descent. The mutation was also absent from MHS individuals in 32 unrelated New Zealand MH pedigrees, including three of Maori origin, as well as 21 unrelated Western Australian pedigrees.

Haplotype analysis

Microsatellite markers flanking the *RYR1* locus and three intragenic RFLP markers were used to analyse the chromosome 19q13.1 genotype in each of the three families.[32–34] This analysis revealed a common haplotype that segregated with MHS in family 1 (Fig. 1A) although the small size of the pedigree prohibited a statistical evaluation. The markers were less informative for the Australian families. However, the 7 allele of the D19S220 marker[32 33] clearly segregated with MHS in the New Zealand kindred (Fig. 1A) but was not present in either of the Australian families (Fig. 1B and C). The D19S47 genotypes were identical (4,8) for the two Australian families and a common allele is shared at the D19S220 locus (6,6 and 3,6) for families 2 and 3, respectively. The RFLP markers were all homozygous for family 2 and all heterozygous for family 3. However, insufficient samples were available for families 2 and 3 to allow phasing of the alleles to be determined, so the genotyping was of limited value.

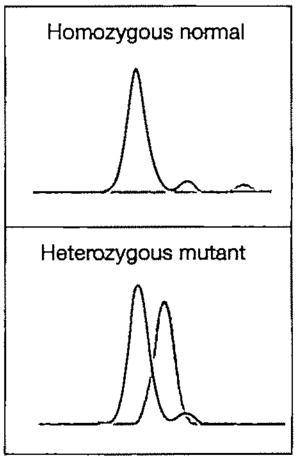

Fig 2 Detection of the C1201T mutation by SNAPshot™ dideoxy primer extension The upper panel shows the normal primer extension product from a homozygous normal control. The lower panel shows two primer extension products from the heterozygous MHS subject.

Diagnostic testing for the C1201T mutation

Dideoxy primer extension (SNAPshot™) was used to distinguish between the normal and mutant allele for family 1. DNA from all individuals known to have the C1201T mutation, as well as from 20 normal samples, was analysed by this method. The heterozygote can be clearly distinguished from the normal homozygote (Fig. 2).

Discussion

Increased E'_{CO_2}, inappropriate sinus tachycardia, muscular rigidity and evidence of muscle breakdown in addition to a rapid increase in temperature are all convincing evidence of a MH reaction in the proband of family 1 (III-1, Fig. 1A). This would achieve a rank of 6 on the MH clinical grading scale,[37] a description of the likelihood that a MH event was 'almost certain'. A strong positive IVCT in the proband and in other family members confirms an MH reaction.

Sequencing of either the entire *RYR1* cDNA or mutation hot-spot regions of the *RYR1* cDNA in three individuals suspected of being MHS has identified a novel C1201T transition that results in an Arg401Cys substitution in the N-terminal region of the RYR. All individuals from the three families investigated who were classified as MHS by IVCT also had the C1201T mutation. This mutation was not found in any of 200 normal individuals or in 32 New Zealand or 21 Australian MH families. These observations strongly suggest that the C1201T mutation is causative of MH in these three families. The mutation is situated two residues upstream of an Ile403Met mutation that has been shown previously to be associated with both MH and CCD in an Italian family.[5] There was no evidence of CCD in any of the pedigrees with the C1201T mutation. Residue Arg401 is strictly conserved across all known sequences from the RYR family (Fig. 3). This, together with the proximity of

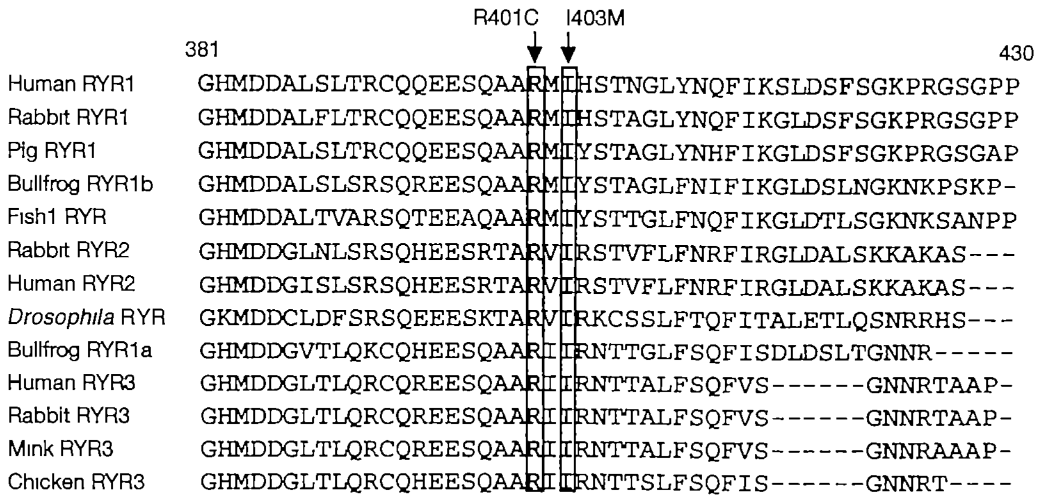
R401C
I403M
381
430
Human RYR1 GHMDDALSLTRCQQEESQAARMIHSTNGLYNQFIKSLDSFSGKPRGSGPP
Rabbit RYR1 GHMDDALFLTRCQQEESQAARMIHSTAGLYNQFIKGLDSFSGKPRGSGPP
Pig RYR1 GHMDDALSLTRCQQEESQAARMIYSTAGLYNHFIKGLDSFSGKPRGSGAP
Bullfrog RYR1b GHMDDALSLSRSQREESQAARMIYSTAGLFNIFIKGLDSLNGKNKPSKP-
Fish1 RYR GHMDDALTVARSQTEEAQAARMIYSTTGLFNQFIKGLDTLSGKNKSANPP
Rabbit RYR2 GHMDDGLNLSRSQHEESRTARVIRSTVFLFNRFIRGLDALSKKAKAS---
Human RYR2 GHMDDGISLSRSQHEESRTARVIRSTVFLFNRFIRGLDALSKKAKAS---
Drosophila RYR GKMDDCLDFSRSQEEESKTARVIRKCSSLFTQFITALETLQSNRRHS---
Bullfrog RYR1a GHMDDGVTLQKCQHEESQAARIIRNTTGLFSQFISDLDSLTGNNR-----
Human RYR3 GHMDDGLTLQRCQREESQAARIIRNTTALFSQFVS------GNNRTAAP-
Rabbit RYR3 GHMDDGLTLQRCQREESQAARIIRNTTALFSQFVS------GNNRTAAP-
Mink RYR3 GHMDDGLTLQRCQREESQAARIIRNTTALFSQFVS------GNNRAAAP-
Chicken RYR3 GHMDDGLTLQRCQHEESQAARIIRNTTSLFSQFIS------GNNRT----

Fig 3 Conservation of R401C and I403M in isoforms of the ryanodine receptor (RyR) The accession numbers are as follows RyR1 human, P21817, RyR pig, P16960, RyR1 rabbit, P11716; RyRa bullfrog, Q91313, RyR1 fish, O13054, RyR3 chicken, Q90985, RyR3 mink, Q95201, RyR3 human, AJ001515; RyR3 rabbit, X68650, RyRb bullfrog, Q91319, RyR2 human, X98330, RyR2 rabbit, Q29621, RyR *Drosophila*, Q24498 Alignments were generated with manually edited FastA outputs using CLUSTALW.

the mutation to the previously reported Ile403Met mutation[5] implies that this residue is functionally significant and is an important region in the MH disorder. Indeed, studies of calcium release using normal and mutant RYR-transfected HEK-293 cells have shown that the Ile403Met mutation is significantly more sensitive to both caffeine and halothane[38] and is associated with higher resting cytoplasmic calcium levels, implying that the mutant channel may be leaky.[39]

The novel *RYR1* mutation discovered in one New Zealand and two Australian MH families could have arisen independently or as a result of a founder effect. To distinguish between these two possibilities, the haplotype at the *RYR1* locus was determined using two highly polymorphic chromosome 19 microsatellite markers (D19S47[34] and D19S220[32,33]) as well as three intragenic RFLP markers.[35] The inheritance of the allele haplotype 7–2–2–1–8 for the markers D19S220, Ile1151, Asp2729, Ser 2862 and D19S47, respectively, coincides with the inheritance of the MHS phenotype in family 1 (Fig. 1A). It is worth noting that the D19S220 allele 7 does not appear in families 2 and 3 (Fig. 1B and C). Without being able to determine chromosome phasing, no definite conclusion can be made concerning relatedness of these two families, but it is possible that the two Australian families share a common haplotype 6–2–2–1–8. If this is the case, a single recombination event could produce the 7–2–2–1–8 haplotype associated with MH in the New Zealand family. However, the probability that two patients with the same haplotype have a common ancestor is inversely related to the frequency of the haplotype in the appropriate general population. The 3 allele has the lowest occurrence of the 10 alleles identified at the D19S220 locus, and the 6 allele is intermediate; the 4 and 8 alleles have the two highest frequencies of the nine alleles reported at the D19S47 locus. In addition, the frequency of recombination is related to the distance between two markers. Since the distance between D19S220 and *RYR1* is ~0.8 centimorgan, recombination can be considered as minimal but cannot be completely ruled out. These observations, together with knowledge of the individual family histories, suggest that the Australian families are unlikely to be related to the New Zealand family and that the mutations have probably occurred independently. More importantly, the discovery of the C1201T mutation in three MH families supports the designation of the MH/CCD region 1 as a mutation hot spot. The C-to-T transition occurs at a CpG dinucleotide, which is a well-known mutation hot spot

In two recent reports EIR has been correlated with mutations in *RYR1* that are also causative of MH [14,15] These are the first reports providing clear evidence of mutations that cause MH also being associated with EIR. Numerous earlier reports have linked EIR with MH susceptibility by demonstrating a positive IVCT.[9,10,40,41] Here we report a novel *RYR1* mutation that has been identified in three separate MHS families, including two where the mutation is associated with EIR. Three siblings of family 1 (Fig. 1A) also had congenital musculoskeletal or connective tissue abnormalities. It is interesting to ask why the C1201T *RYR1* mutation appears to provide different phenotypes, that is MH alone, MH plus congenital abnormalities, or MH with EIR. It is possible that other genetic factors contribute to different MH phenotypes, as proposed by Robinson and colleagues.[42] The *RYR1* defect could account for the MHS phenotype, while a mutation within another gene could modify this phenotype to produce either EIR or other musculoskeletal abnormalities. Clear evidence of the same *RYR1* defect producing different phenotypes has been provided in the case of CCD and MH.[21] Considering the variable penetrance of clinical MH, it is highly likely that modifier genes have an important role to play in this complex genetic disorder.

Congenital musculoskeletal and connective tissue abnormalities have been linked previously to MH susceptibility.[43] Britt and Kalow[43] noted a high incidence of abnormalities, including cramps, strabismus, hernia, hare lip and cleft palate, clubfoot, kyphoscoliosis, recurrent dislocating patella and other orthopaedic abnormalities. More recently, however, a prospective Scandinavian study of 210 patients investigated for MH found no significant increase in the incidence of congenital musculoskeletal or connective tissue abnormalities.[44] In addition, Larach compared 198 patients with positive MH biopsies with 849 normal individuals with no personal or family history of MH, and found a similar incidence of muscle cramps in the two groups.[45] Larach and colleagues also analysed 178 patients experiencing very likely or almost certain MH events and found a 22% incidence of musculoskeletal abnormalities, which included problems with muscle tone.[46] The findings from a study of 400 patients undergoing IVCT in New Zealand indicate a low incidence of abnormalities (Pollock N; unpublished data).

Many of the abnormalities reported by Britt and Kalow[43] occur with some frequency in the general population, and results of the later studies question whether an increased incidence of abnormalities exists in MHS individuals. However, these were largely retrospective studies and a large prospective study comparing MHS and MH normal individuals is required. MH-type reactions have, however, been reported in rare skeletal and connective tissue syndromes with genetic abnormalities.[47–50] Reactions have also been reported in families with musculoskeletal and connective tissue problems that affect multiple individuals,[51–54] with possible associated genetic abnormalities, as in family 1. In addition, the non-specific myopathic changes observed in families 2 and 3, as well as the incidence of EIR where there was also no known family history of MH suggest that an awareness of the possibility of an MH reaction in each of these groups may need to be exercised.

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Comparison of mepivacaine and lidocaine for intravenous regional anaesthesia: pharmacokinetic study and clinical correlation

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Background. Limitations to the use of lidocaine for intravenous regional anaesthesia (IVRA) include lack of optimal intraoperative analgesia and systemic toxic reactions.This randomized double-blind study was conducted to compare intraoperative and postoperative analgesia, adverse effects, and plasma concentrations of mepivacaine or lidocaine, on release of the tourniquet in patients undergoing IVRA for distal upper limb surgery.

Methods. Forty-two adult patients were randomly allocated to receive either a 0.5% lidocaine solution 3 mg kg^{-1} (*n*=20) or mepivacaine 5 mg kg^{-1} (*n*=22). Plasma concentrations of both anaesthetic agents were measured at 5, 10, 20, 30, 45, and 60 min after deflation of the tourniquet by gas chromatography.

Results. Although plasma concentrations of mepivacaine and lidocaine were comparable 5 min after deflation, concentrations of lidocaine decreased significantly thereafter, whereas plasma concentrations of mepivacaine were similar over the 60-min study period. Supplementary analgesia during the intraoperative period was required by 45% of patients in the lidocaine group as compared with 9% in the mepivacaine group (*P*=0.02). No adverse effects were observed in patients given mepivacaine. In the lidocaine group, adverse effects were observed in 10% of the patients. The total ischaemia time, volume of the local anaesthetic, and duration of the surgical procedure were not significantly different between the two groups.

Conclusions. Mepivacaine 5 mg kg^{-1} ensured better intraoperative analgesia than lidocaine 3 mg kg^{-1} when used for IVRA. Plasma concentrations of lidocaine decreased significantly between 5 and 60 min following tourniquet deflation, whereas blood concentrations of mepivacaine remained below the toxic concentration.

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Intravenous regional anaesthesia (IVRA) is a simple and effective technique for distal upper limb surgery of less than 1 h duration.[1] Some clinical studies have recently shown that the addition of a non-steroidal anti-inflammatory agent,[2] an opioid,[3] neuromuscular blocking agents,[4] clonidine,[5] and even ketamine[6] to lidocaine can improve the quality of the regional anaesthesia. Although lidocaine is one of the least toxic local anaesthetics, in our experience, limitations to its use include lack of optimal intraoperative analgesia and systemic toxic reactions. In our clinical experience of more than 10 yr, we found that the use of mepivacaine 5 mg kg^{-1} for IVRA was a satisfactory alternative to the classical IVRA technique and that systemic reactions after tourniquet deflation did not occur. Therefore, a randomized double-blind study was designed to compare IVRA using lidocaine or mepivacaine in

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Table 1 Patient characteristics and data of the anaesthetic technique and surgical procedure *$P<0.05$

	Mepivacaine	**Lidocaine**
Patients (no.)	22	20
Age (yr)	47.4 (22–78) *	57.9 (31–85) *
Sex (male/female)	7/15	7/13
Weight (kg)	70.72 (17.6)	71.45 (15.4)
Height (cm)	162 (10)	158 (7)
Volume local anaesthetic (ml)	36.7 (3.4)	37.7 (3.3)
Time of ischaemia (min)	43.5 (8.4)	40.8 (4.6)
Duration of surgery (min)	19.1 (13.6)	17.3 (9.0)
Carpal tunnel/other procedures of forearm and hand	13/9	14/6

forearm and hand surgery. Plasma concentrations of the drugs on release of the tourniquet, intraoperative and postoperative analgesia and adverse effects were determined.

Methods

The procedure for this study was approved by the Ethics Committee of the hospital. Informed consent was obtained. Forty-two adult ASA physical status I or III patients of both sexes undergoing elective minor forearm and hand surgery gave written informed consent to participate in this prospective double-blind study. Patients with liver disorders, history of allergic reaction to local anaesthetics, those not wishing the IVRA technique, or in whom venipuncture was difficult were excluded. Patients were allocated to one of two groups according to a table of random numbers. Patients in one group (n=22) received 0.5–1% mepivacaine 5 mg kg^{-1} up to a maximal dose of 400 mg and maximal volume of 40 ml, whereas those in the other group (n=20) received 0.5% lidocaine 3 mg kg^{-1} up to a maximal dose of 400 mg and maximal volume of 40 ml.

Patients ≤50 kg and/or with respiratory disease were premedicated with diazepam 5 mg, whereas patients weighing greater than 50 kg were given diazepam 10 mg. A 20-gauge catheter was introduced into a vein on the dorsum of the hand to be operated upon and another 16-gauge catheter was inserted into a vein of the arm not requiring surgery for fluid infusion and blood sampling. The operative arm was exanguinated by elevating it and wrapping it with a rubber Esmarch bandage. The proximal cuff of a double tourniquet was then inflated to 350 mm Hg and 20 ml min^{-1} of either mepivacaine or lidocaine was injected in a double-blind fashion into the indwelling cannula. After approximately 15 min, the distal cuff was inflated to the same pressure. A minimum total ischaemia time of 40 min was established for safety reasons because of the use of mepivacaine in doses much larger than those reported in the literature. Midazolam 1 mg every 10 min up to a maximum of 5 mg was used for intraoperative sedation trying to maintain the patient at level 2–3 on the Ramsay sedation scale.[7] Supplementary intraoperative analgesia consisted of intravenous boluses of fentanyl 50 µg every 10 min up to a total dose of 150 µg. Boluses of fentanyl were provided whenever there was a 20% increase in baseline values of arterial pressure and/or heart rate or when analgesia was graded as poor by the patient. Patient's vital signs (arterial pressure, ventilatory frequency, pulse oximeter), analgesic request, and presence of adverse events related to unexpected deflation of the tourniquet were assessed intraoperatively.

Venous blood samples were obtained from the opposite arm at 5, 10, 20, 30, 45, and 60 min after release of the tourniquet. The samples were centrifuged and the plasma frozen at −20°C and stored. Plasma concentrations of local anaesthetics were analysed by gas chromatography/mass spectrometry.

After tourniquet release and at the end of surgery, patients were asked to report any adverse effects. Symptoms of dizziness, nystagmus, tinnitus, facial dysaesthesia, convulsions, depression of the central nervous system, bradypnoea (ventilatory frequency ≤10 breaths min^{-1}), bradycardia (heart rate ≤50 beats min^{-1}), and cardiovascular depression (≤25% decrease in baseline arterial pressure) were noted, if present. Patient's vital signs and time to the first analgesic request after cuff release (time of residual analgesia) were recorded in the postanaesthesia care unit.

The sample size was calculated according to the main objective of the study, that is adequate intraoperative analgesia with mepivacaine for IVRA, which was determined by the need for supplementary medication intraoperatively, for a sensitivity of 20%, beta error of 0.10 and an alpha error of 0.05. Patient characteristics and data related to the anaesthetic technique and the surgical procedure were recorded in both groups. Comparison of categorical variables was carried out with the Pearson's chi-squared test. All quantitative variables with the exception of time of residual analgesia were normally distributed and were analysed using the Student's t-test if variances were comparable or with the Mann–Whitney U test if variances were not comparable. Paired data were analysed with the paired t-test. Kaplan–Meier survival analysis was performed for time of residual analgesia. Statistical analysis was performed with the SPSS/PC+ (version 8.0, SPSS Inc., Chicago, IL) software programme. Data are expressed as mean (SD) unless indicated otherwise.

Table 2 Plasma concentrations of mepivacaine and lidocaine (μg ml^{-1}) during the observation period at the of surgery *$P<0.05$

Blood sampling after surgery	Mepivacaine (n=22)	Lidocaine (n=20)
5 min	1.60 (0.52)	1.68 (0.73)*
10 min	1.70 (0.51)	1.37 (0.48)
20 min	1.77 (0.47)	1.11 (0.30)
30 min	1.69 (0.42)	0.98 (0.26)
45 min	1.72 (0.48)	0.86 (0.23)
60 min	1.68 (0.41)	0.81 (0.21)*

Results

Patients characteristics and data of the anaesthetic and surgical techniques in both study groups are shown in Table 1. There were no statistically significant differences in relation to weight, height, gender, volume of local anaesthetic agent used, time of ischaemia, duration of operation, and type of surgical procedure. However, patients in the mepivacaine group were significantly younger (47.4 (22–78) yr) than those in the lidocaine group (57.9 (31–85) yr) (P=0.04).

Intraoperative analgesia was significantly better amongst mepivacaine-treated patients because supplementary analgesia with fentanyl was required by 9% of patients in the mepivacaine group as compared with 45% in the lidocaine group (P=0.02). Median times required for supplementary analgesia were 35 min (95% confidence interval (CI) 18–52 min) in the mepivacaine group and 30 min (95% CI 19–41 min) in the lidocaine group. With regard to the frequency of adverse events on release of the tourniquet, no adverse effects were observed in patients given mepivacaine, whereas in the lidocaine group, transient bradycardia, and dizziness were experienced by one patient each within 5 min after tourniquet deflation.

Plasma concentrations of both local anaesthetic agents are shown in Table 2. Five minutes after cuff deflation, plasma concentrations of mepivacaine and lidocaine were comparable. However, plasma concentrations of lidocaine decreased significantly between 5 and 60 min following tourniquet deflation ($P<0.001$), whereas blood concentrations of mepivacaine did not change during the observation period. At 60 min, plasma concentrations of mepivacaine were significantly higher than those of lidocaine ($P<0.001$).

Discussion

Different anaesthetic agents including procaine, lidocaine, and prilocaine[8] have been used for IVRA since the initial description of this technique by Bier in 1908. Research in this field has been focused on the search for the ideal agent for IVRA that would be the one with which adequate intraoperative analgesia is attained, but without the systemic toxicity in the event of tourniquet release. The inadvisability of using bupivacaine for IVRA is related to the sudden occurrence of dangerous cardiotoxicity,[9–11] whereas the use of chloroprocaine in IVRA ceased after reports of hypersensitivity reactions and postanaesthetic thrombophlebitis.[12] The ideal anaesthetic agent for IVRA would be the one that had the requisite degree of local anaesthetic activity, but with low cardiovascular and central nervous system toxicity. Lidocaine is probably the local anaesthetic most commonly chosen for this technique,[13 14] although prilocaine is better tolerated in terms of systemic toxicity than lidocaine.[15]

The dose of lidocaine recommended for classical IVRA technique (3 mg kg^{-1} as a 0.5% lidocaine solution) was used. With respect to mepivacaine, we used a dose of 5 mg kg^{-1} with which consistent satisfactory results had been obtained by our group as well as by others.[16 17] According to the study of Rawal and co-workers[18] in which plasma concentrations of mepivacaine, lidocaine, and prilocaine when given at the 3 mg kg^{-1} dose peaked within 5 min after tourniquet release, we decided to start measurements of plasma drug concentrations at 5 min following tourniquet deflation, with the last measurement at 60 min because in the pharmacokinetic study of Simon and associates[8] less than 1 μg ml^{-1} of lidocaine was measured from that time. Although in the case of mepivacaine for IVRA, no previous studies have evaluated plasma concentrations of this agent at 60 min after deflation, a pharmacokinetic behaviour similar to that of lidocaine was assumed as in the study of Rawal and co-workers,[18] mepivacaine and lidocaine showed similar pharmacokinetics 5 min after tourniquet release.

As compared with lidocaine, mepivacaine 5 mg kg^{-1} provided better intraoperative analgesia with no adverse effects on release of the tourniquet. Moreover this finding is supported by plasma concentrations of the drugs that were comparable 5 min after deflation (1.68 (0.73) μg ml^{-1} for lidocaine and 1.62 (0.52) μg ml^{-1} for mepivacaine), whilst plasma concentrations of lidocaine decreased significantly (0.81 (0.21) μg ml^{-1}) at 60 min as opposed to plasma concentrations of mepivacaine that did not vary (1.68 (0.41) μg ml^{-1}). The observation of similar plasma concentrations of both anaesthetic agents despite the use of almost double concentrations of mepivacaine may be explained by the vascular effects of mepivacaine (vasoconstriction) in IVRA[19] and a much more sustained release to the systemic circulation as compared with the predominatly vasodilatory effects of lidocaine.[20] Therefore, toxic plasma concentrations of mepivacaine are not reached rapidly as opposed to lidocaine 3 mg kg^{-1} when adverse events may appear within the first minute after tourniquet release as reported by Simon and associates.[8] On the other hand, the relatively prolonged nature of the increase in systemic mepivacaine concentrations might produce longer term psychometric effects. However, we did not examine this in our study.

Up to the present time, toxic plasma concentrations of local anaesthetics greater than 4 μg ml^{-1} for lidocaine and between 5 and 6 μg ml^{-1} for mepivacaine have been quoted.[13] In our study, however, plasma drug concentrations within the first 5 min after tourniquet release were not measured but in that interval a case of dizziness and a case of bradycardia occurred. No patient in the lidocaine group showed plasma concentrations greater than 3 $\mu g\ ml^{-1}$, although there was a greater dispersion of lidocaine values at 5 min (predominately 2–3 $\mu g\ ml^{-1}$). In our study, there were no statistically significant differences in the occurrence of adverse events, probably because of the small sample size. In the study of Simon and co-workers,[8] five of the 10 patients showed plasma concentrations of lidocaine greater than 4 $\mu g\ ml^{-1}$ during the first minute after release of the tourniquet. This is in contrast to findings of Rawal and associates[18] who reported plasma concentrations of lidocaine less than 1 $\mu g\ ml^{-1}$ at this time. It should be noted, however, that in the first study[8] high-performance liquid chromatography was used for the assessment of plasma drug concentrations in 10 patients, whereas in the second study[18] gas chromatography in 20 patients. In the study of Simon and co-workers,[8] although toxic plasma concentrations were obtained in half of the patients, none of them experienced any adverse effect. In contrast, in the study of Rawal and colleagues,[18] four patients in the lidocaine group experienced dizziness as compared with none in the mepivacaine group.

This preliminary study in a small number of patients indicates that mepivacaine 5 mg kg^{-1} has a closer profile of the ideal local anaesthetic agent for IVRA than lidocaine 3 mg kg^{-1}. Mepivacaine offered adequate intraoperative analgesia with no incidence of adverse effects on release of the tourniquet despite persistence of plasma drug concentrations during the 60-min study period.

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Effect of perioperative administration of dexketoprofen on opioid requirements and inflammatory response following elective hip arthroplasty

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Background. In this double-blind, randomized, placebo-controlled trial, the safety and analgesic efficacy of perioperative dexketoprofen were evaluated.

Methods. Thirty ASA I or II patients undergoing elective hip arthroplasty were randomized to one of two groups. One group (D) received dexketoprofen 25 mg tds for 24 h before and 48 h after surgery; the second group (P) received placebo tablets at equivalent times. Hyperbaric 0.5% bupivacaine (17.5 mg if greater than 70 kg and 15 mg if less than 70 kg) and preservative-free morphine (0.6 mg) were administered intrathecally. Postoperatively, PCA was provided (bolus morphine sulphate 1 mg; lockout 5 min; no continuous infusion).

Results. The two groups were similar in terms of age, gender, weight, height, ASA class, duration of operation, and level of sensory block on arrival to the recovery room. Groups were also similar in terms of blood loss, transfusion requirements, ventilatory frequency, and haemodynamic variables. According to visual analogue pain scores patients in group D experienced less pain at 15 h (P=0.02) postoperatively. Cumulative morphine consumption was also less in group D compared with group P at 6 (0.06 (0.2) *vs* 0.85 (1.4) mg, P=0.04) and 48 h postoperatively (10.1 (8) *vs* 26.2 (20) mg, P<0.01). Plasma interleukin 6 concentrations increased postoperatively to a significantly lesser extent in group D than in group P (P=0.02). Nausea and vomiting were less (P<0.01) in group D compared with group P at 18 h postoperatively. Sedation scores were less (P=0.03) in group D.

Conclusions. Perioperative administration of dexketoprofen 25 mg 8 hourly markedly improves analgesia and decreases opioid requirements (and associated adverse effects) following hip arthroplasty. It appears that this regimen decreases the postoperative pro-inflammatory response.

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Administration of non-steroidal anti-inflammatory drugs (NSAID) and opioids in combination for postoperative pain following major orthopaedic surgery is routinely practiced but incompletely effective.[1] The potential to enhance analgesia and decrease opioid adverse effects justifies continued efforts to identify the optimal combination, mode of administration, and timing of administration of these drugs.

Dexketoprofen trometamol, the active enantiomer of racemic ketoprofen, is a relatively new oral NSAID with analgesic and anti-pyretic properties. The advantages of this product compared with ketoprofen are faster onset of action, increased potency, and possibly decreased potential for gastrointestinal side effects.[2 3] Early studies indicate that dexketoprofen is effective and well tolerated in clinical practice.[4] Dexketoprofen 25 mg tds has greater analgesic efficacy and fewer side effects than racemic ketoprofen in patients with osteoarthritis of the knee.[5] Dexketoprofen trometamol possesses characteristics which may be of particular benefit to patients during the perioperative period.

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Its cyclo-oxygenase inhibitory effects decrease arachidonic acid metabolism to PGE_1, PGE_2, PGF_1, $PGF_2\alpha$, and thromboxanes A_2 and B_2, which accounts in part for its analgesic effects. To date, its analgesic efficacy has been established for patients with postoperative dental pain.[6] Its optical isomer, R(–)-ketoprofen, is not only pharmacologically inactive as a COX inhibitor, but endowed with toxic potential, especially in terms of prostaglandin-independent ulcerogenity (possibly related to neutrophil margination).[7]

Hip arthroplasty is routinely performed with a regional anaesthetic technique by administering a combination of hyperbaric bupivacaine and morphine intrathecally. This provides excellent conditions for surgery and appears to give satisfactory analgesia in the early postoperative period. However, clinical observation indicates that a period of inadequate analgesia often occurs between the offset of intrathecal opioid effect and the onset of effect of systemically administered opioids. Typically, this interval occurs 12–24 h postoperatively.

We hypothesized that the perioperative administration of dexketoprofen 25 mgs tds orally to patients undergoing elective hip arthroplasty under spinal anaesthesia would decrease the postoperative opioid requirements and attenuate the perioperative inflammatory response. To test this hypothesis, we carried out a prospective randomized, double-blinded, controlled clinical trial in patients undergoing hip arthroplasty under spinal anaesthesia with perioperative administration of dexketoprofen or placebo.

Methods

With institutional ethical approval and written informed patient consent, 30 ASA I or II patients aged 45–70 yr undergoing elective hip arthroplasty under spinal anaesthesia were studied. Patients with chronic illnesses other than osteoarthritis or who had recent (2 months) surgery or infection, patients receiving concurrent medication with NSAID or with drugs known to interact with NSAID, patients with allergies or contraindications to NSAID or opioids were excluded.

Patients were randomly allocated to two groups: one group (D) received dexketoprofen 25 mg tds for 24 h before and 48 h after surgery; the second group (P) received a placebo tablet at equivalent times. As the interval from a single preoperative dose of dexketoprofen to the surgical incision may vary in practice between 1 and 2 h, the result would be markedly different dexketoprofen plasma concentration during surgery. In order to minimize this variability, the trial drug was administered for 24 h preoperatively.

All patients were instructed in the use of the Vygon patient-controlled pump and the use of the visual analogue scale for pain assessment. Patients received diazepam 10 or 15 mg 1 h preoperatively, if this was deemed appropriate by the anaesthetist.

On arrival to the operating room, standard monitoring was established (pulse oximetry, ECG, non-invasive arterial pressure monitoring with a Datex AS/3, Dale Corp., Madison, WI, USA Monitor). A 14G cannula was sited in a peripheral vein under local anaesthesia (2% lidocaine) in the non-dominant forearm and an infusion of compound sodium lactate 1000 ml commenced, of which 500 ml was administered rapidly. Patients were then placed in the lateral position with the operative site dependent. Using standard aseptic technique, the third and fourth lumbar interspace was located with palpation and infiltrated with 2% lidocaine (23G needle). Hyperbaric bupivacaine 0.5% (17.5 mg if greater than 70 kg and 15 mg if less than 70 kg) and preservative-free morphine (0.6 mg) were administered intrathecally through a 25G Whitacre B-D spinal needle (Becton Dickinson and Co., Franklin Lakes, NJ, USA). Sensory block was assessed during the subsequent 5–10 min using ethyl chloride spray. Postoperatively, all patients had access to disposable Vygon PCA pump (bolus 1 mg; lockout 5 min; no continuous infusion) (Laboratoires Pharmaceutique Vygon, Ecouen, France). Cyclizine 50 mg i.m. prn 8 hourly was prescribed for nausea and vomiting. The level of sensory block was again assessed on arrival to the postanaesthesia care unit. Intraoperative and total blood loss were estimated (by weighing swabs) and transfusion of blood products were also recorded.

Venous blood samples (10 ml) were withdrawn for estimation of plasma concentration of urea, creatinine, liver function tests, and the pro-inflammatory interleukin 6 (IL-6) on five occasions: 24 and 18 h preoperatively and 6, 24, and 48 h postoperatively. The samples for estimation of plasma IL-6 concentration were collected in sterile EDTA tubes, centrifuged at 1000 *g*, and the supernatant stored at –80°C. Plasma IL-6 concentration was measured using specific enzyme linked immunosorbent assays (ELISA) with specific polyclonal rabbit antibodies to recombinant IL-6 commercial kits (R&D System, Abingdon, Oxon, UK).

At 24 and 18 h preoperatively and at 2, 6, 12,15,18, 24, and 48 h postoperatively the following data were collected: heart rate, ventilatory frequency, temperature, and arterial pressure; pain (visual analogue scale); cumulative opioid consumption; adverse effects associated with opioid administration. (i) Nausea, vomiting (1, no nausea; 2, complaints of nausea but tolerable; 3, needs cyclizine 50 mg i.m.); (ii) respiratory depression (ventilatory frequency less than 8 $\min^{-1}$); (iii) pruritus (1, no itch; 2, itching but tolerable; 3, severe itch needs piriton 5 mg i.m.); (iv) sedation (1, awake; 2, drowsy; 3, asleep, easily rousable; 4, asleep, hard to rouse); (v) urinary retention (C, catheterized electively postoperatively; N, no catheter required; R, catheter sited because of urinary retention). In addition, adverse effects associated with dexketoprofen administration, that is dyspepsia, heartburn, abdominal pain, headache, and dizziness were noted.

Previous data on patients who had received a spinal anaesthetic with bupivacaine and morphine for joint replacement and morphine PCA for 24 h postoperatively showed a mean morphine consumption of 20 (SD 9.75) mg.[8] It was calculated that 26 patients (13 pairs) would be required to have an 80% power of detecting a 50% reduction in the 24 h morphine consumption at a significance level of 0.05.

Statistical analyses were undertaken with StatView 4.5 for Windows (1992–1996). Data on patients' weight and height, operating time, total blood loss, and transfusion requirements were analysed using Student's *t*-test. $P<0.05$ was considered significant. Repeated measures ANOVA was used to compare morphine consumption, VAS for pain and sedation, IL-6 concentrations, pruritus, postoperative nausea and vomiting, biochemistry, and physiological parameters. Fisher's exact test was used to compare non-parametric data (i.e. necessity of a urinary catheter). $P<0.05$ was considered significant.

Table 1 Patient characteristics, duration of surgery, and the upper level of sensory block on arrival to recovery

	Group P (n=15)	Group D (n=15)
Age (yr) (range)	60.0 (45–69)	65.0 (46–70)
Weight (kg)	80.9 (12 3)	78 1 (17 5)
Height (cm)	170 3 (7 9)	170.7 (7.9)
Male·female ratio	8 7	9.6
ASA I II	11 4	11·4
Surgical time (min)	75 9 (25.1)	78 0 (27 1)
Upper level of sensory block on arrival to recovery	T8 (T6, T12)	T8 (T4, T10)

Table 2 Blood loss and transfusion requirements. Data are mean (SD)

	P (n=15)	D (n=15)
Intraoperative blood loss (ml)	623.7 (612)	616 (366)
Total blood loss (ml)	1035 (787)	1103 (421)
Total actual blood loss (litre)	15 518	15.979
Total packed red cells transfused (litre)	2.750	2 750

Table 3 Ventilatory frequency. Data are mean (SD) *$P<0.05$ compared with the preoperative baseline. No difference between groups was found

Measurement time point	Placebo group (n=14)	Dexketoprofen group (n=15)
Preoperative		
24 h	18 0 (1 5)	18.0 (1.5)
18 h	17 7 (2 1)	6.9 (3.2)
Postoperative		
2 h	16.8 (2.0)	16 8 (1.2)*
6 h	17.0 (1.7)	16.0 (3.0)*
12 h	17 0 (2.0)	17 0 (2 1)*
15 h	17 1 (2 3)	16.8 (1 8)*
18 h	17 0 (1 9)	17 0 (1.8)*
24 h	17 1 (1 2)	17.5 (1.7)
48 h	17 1 (1 2)	17 3 (1.4)

Results

The two groups were similar with respect to age, gender, weight, height, ASA class, duration of surgery, and level of sensory block on arrival to recovery room (Table 1). One patient in the placebo group was excluded as he received diclofenac 100 mg pr intraoperatively. Groups were also similar in terms of intra- or postoperative blood loss and in the transfusion requirements (Table 2), ventilatory frequency (Table 3), or haemodynamic variables (Table 4).

Cumulative morphine consumption was less in group D compared with group P at 6 (0.06 (0.2) *vs* 0.85 (1.4) mg, P=0.04) and 48 h postoperatively (10.1 (8) *vs* 26.2 (20) mg, $P<0.01$) (Fig. 1). The time to first analgesia postoperatively was significantly greater in group D (1277 (1031) min) than group P (642 (317) min) (P=0.03). Figure 2 displays the VAS scores for pain recorded at the time points mentioned. Although patients in group D tended to experience less pain throughout the postoperative period, this achieved statistical significance only at 15 h (P=0.02) postoperatively. Plasma IL-6 concentrations were less in group D than in group P at 6 h (94.4 (70) *vs* 162 (83) pg ml^{-1}, P=0.02) but not at 24 and 48 h postoperatively (Fig. 3).

Nausea and vomiting were less ($P<0.01$) in group D compared with group P at 18 h postoperatively (Fig. 4). Patients in both groups experienced pruritus, which was greatest in intensity 2 and 6 h postoperatively (Fig. 5).

Table 4 Haemodynamic measures Data are mean (SD) *$P<0$ 05 refers to comparison with the preoperative baseline No difference between the groups

Measurement time point	Placebo group (n=14)		Dexketoprofen group (n=15)	
	Systolic arterial pressure	Diastolic arterial pressure	Systolic arterial pressure	Diastolic arterial pressure
Preoperative				
24 h	126 (13)	75 (10)	133 (12)	80 (6)
18 h	124 (14)	75 (9)	133 (11)	79 (7)
Postoperative				
2 h	104 (12)*	61 (9)*	106 (30)*	65 (9)*
6 h	109 (12)*	65 (7)*	110 (14)*	60 (11)*
12 h	114 (14)*	64 (7)*	111 (15)*	62 (11)*
15 h	113 (17)*	62 (10)*	104 (31)*	62 (10)*
18 h	118 (21)	64 (12)*	110 (13)*	63 (8)*
24 h	119 (10)	67 (9)*	116 (10)*	67 (9)*
48 h	125 (13)	73 (6)	120 (11)*	68 (9)*

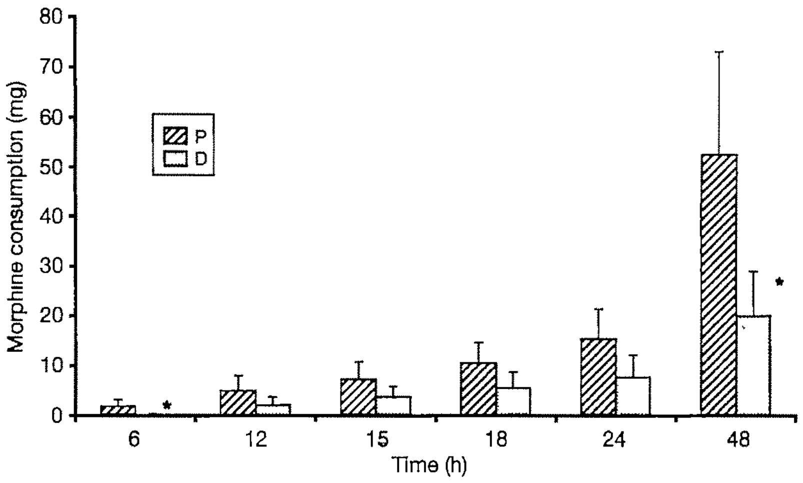

Fig 1 Data are mean (SD) *$P<0.05$ refers to between groups comparisons. P, placebo group; D, dexketoprofen group

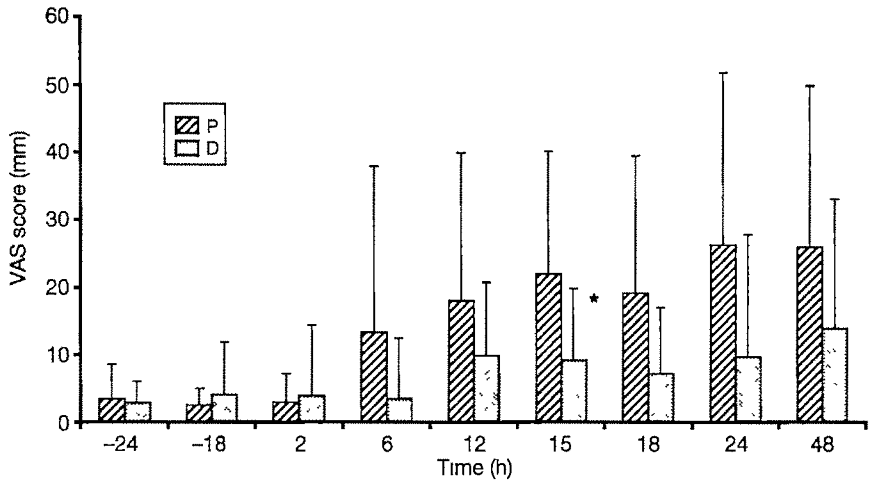

Fig 2 Data are mean (SD) *$P<0.05$ refers to between groups comparisons. P, placebo group; D, dexketoprofen group.

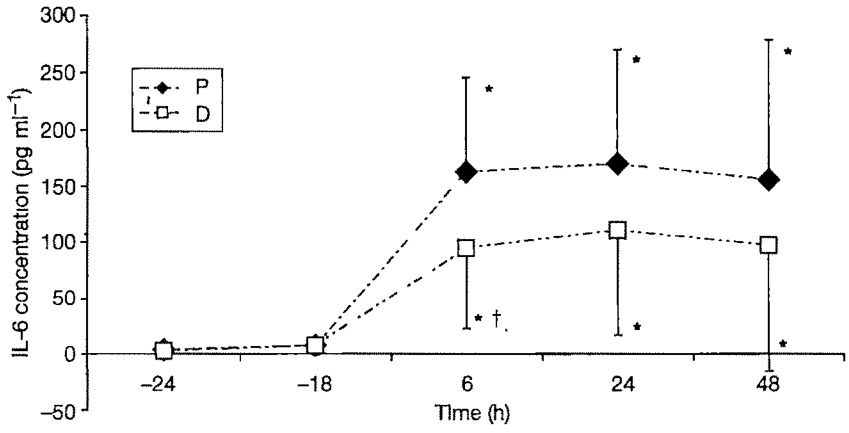

Fig 3 Data are mean (SD) *$P<0.05$ refers to comparison with the baseline †$P<0.05$ refers to between groups comparisons P, placebo group, D, dexketoprofen group

Sedation scores were increased compared with the baseline in group D at 2 and 6 h ($P<0.01$) postoperatively and in group P at 12, 15, and 18 h ($P<0.01$) postoperatively. At 18 h postoperatively, sedation scores were less in group D than in group P ($P=0.03$) (Fig. 6). Seven patients in each group were electively catheterized postoperatively. However,

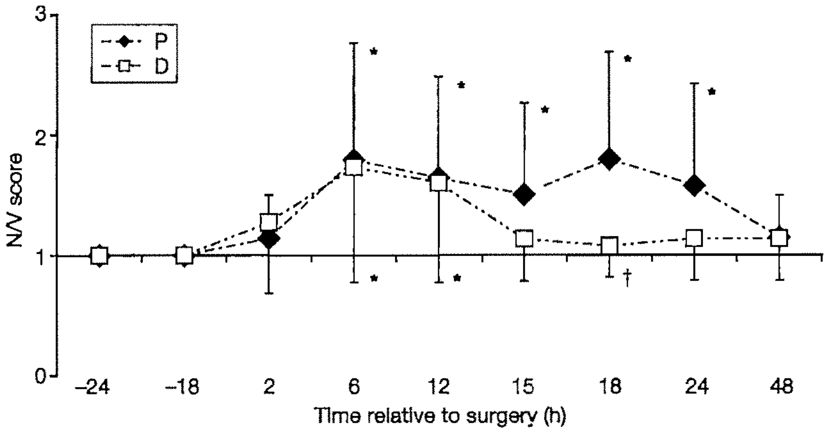

Fig 4 Data are mean (SD). *$P<0.05$ refers to comparison with the baseline. †$P<0.05$ refers to between groups comparisons P, placebo group, D, dexketoprofen group

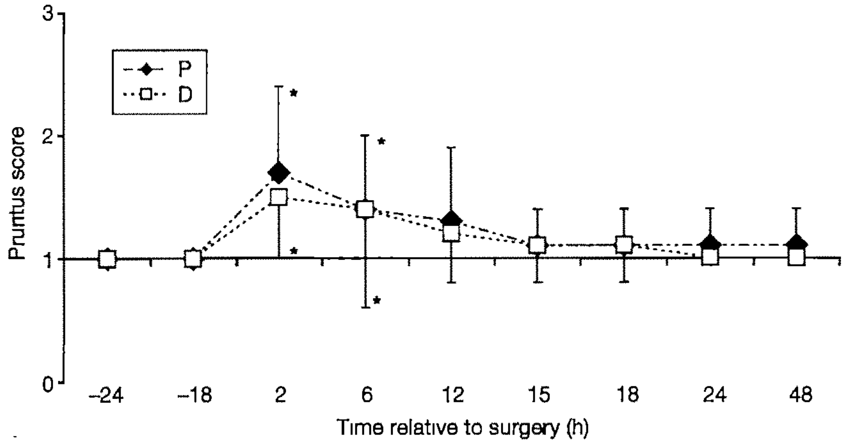

Fig 5 Data are mean (SD) *$P<0.05$ refers to comparisons to the baseline P, placebo group, D, dexketoprofen group

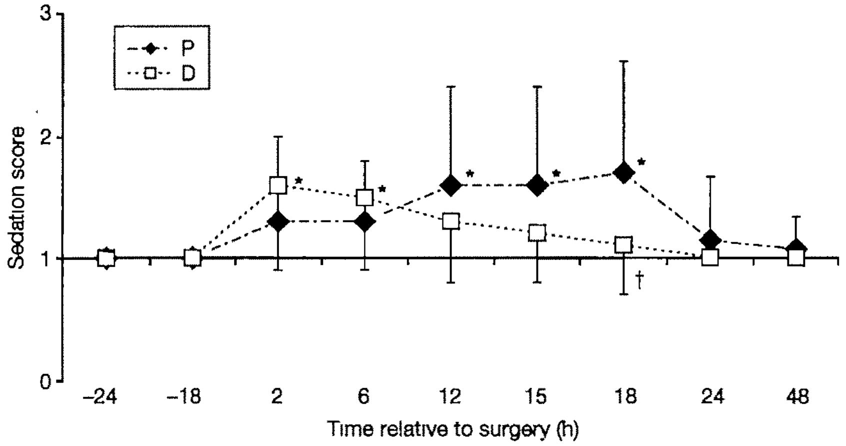

Fig 6 Data are mean (SD). *$P<0.05$ refers to comparisons to the baseline. †$P<0.05$ refers to comparison between the two groups. P, placebo group, D, dexketoprofen group

three patients in group P were catheterized on a total of four occasions for urinary retention. Only one patient in group D required catheterization for this reason.

The renal (urea, creatinine, potassium plasma concentration) and hepatic (ALT, total bilirubin, alkaline phosphatase) profiles were normal in all patients at each time point.

No complication or side effect attributable to dexketoprofen (dyspepsia, heartburn, abdominal pain, headache, dizziness, diarrhoea, constipation, paraesthesia, skin rash) was reported.

Discussion

Ketoprofen is well established as an effective analgesic and anti-inflammatory agent in the treatment of conditions such as rheumatoid arthritis, osteoarthritis, and mild to moderate pain from a variety of causes.[9] However, this compound is a racemic mixture of two stereoisomers, of which only the dextro-rotatory enantiomer, dexketoprofen, has biologic activity. Therefore, dexketoprofen potentially offers several advantages over the racemic parent drug. In humans, the relative bioavailability of oral dexketoprofen trometamol (12.5 and 25 mg, respectively) is similar to that of oral racemic ketoprofen (25 and 50 mg, respectively), as measured in all cases by the area under the concentration-time curve values for S(+)-ketoprofen.[2] Similarly, the activity of dexketoprofen was twice that of racemic ketoprofen in all models investigated. Thus, the pure enantiomer may be administered at half the dosages of the racemic compound analgesic (12.5 and 25 *vs* 25 and 50 mg, respectively), which reduces the hepatic metabolic load and the total amount of metabolites formed.[2]

Use of a single enantiomer simplifies the pharmacokinetic profile of the compound by eliminating enantiomer inversion; therefore, dexketoprofen has the potential to decrease pharmacokinetic variability compared with racemic ketoprofen.[9] Trometamol was added to dexketoprofen to increase solubility more than 1000-fold compared with the free acid form. It has been shown that its absorption after oral administration is much faster ($t_{\max}$ 0.25–0.75 h) and consistent than after the administration of either dexketoprofen-free acid or racemic ketoprofen ($t_{\max}$ 0.5–3 h). Its half-life is 1–4 h, distribution volume 0.1–0.2 litre kg^{-1}, with greater than 99% plasma protein binding. Excretion is predominantly by urinary route, with glucuronide conjugates accounting for 90% of the administered dose. There is neither metabolic inversion of the active S(+)-enantiomer (eutomer) to its essentially inactive optical opposite (distomer), nor incorporation into fat tissue.[7]

In the past, i.m. 'prn' opioids were routinely prescribed for postoperative analgesia and often provided suboptimal analgesia and considerable morbidity. Currently, regional anaesthetic techniques, epidural and intrathecal opioids, and combinations of these are routine components of anaesthetic practice. It is likely that the benefits of providing adequate analgesia postoperatively extends beyond patient satisfaction and also leads to improved patient outcome.[10] The concept of combining an opioid with a non-sedating, non-opioid analgesic is a simple form of multimodal therapy. The aim of such a combination is to make use of the synergism between the analgesic effects of the individual drugs.[11–13] Advantages also include decreased opioid requirements and thus associated adverse effects.

Timing of NSAID administration is clinically important because the onset of effect of these drugs is 30–60 min following oral administration. Their opioid sparing effect is not apparent until 4 h after oral administration.[14] In experimental studies, the evidence favouring pre-emptive analgesia is very convincing. However, clinical studies have produced conflicting results possibly because of differing study designs.[15] In this study, the trend towards opioid sparing was apparent throughout the postoperative period, although it reached statistical significance only at 6 and 48 h. The time to first (opioid) analgesia was 1277 (1031) min in group D *vs* 642 (317) min in group P (P=0.03), which in group D is well beyond the offset of intrathecal opioid effect.

The current investigation addressed two questions. (i) Does perioperative dexketoprofen administration possess opioid sparing effects in the postoperative period? (ii) Does perioperative dexketoprofen administration influence the perioperative pro-inflammatory state as assessed by the plasma IL-6 concentration?

The most important finding of the study is the marked reduction in postoperative opioid requirements, followed by decrease in postoperative nausea and vomiting, sedation, urinary retention, and prolongation of time to first analgesia with no evident complications or adverse effects.

Secondly, the perioperative pro-inflammatory state was attenuated as shown by the decreased IL-6 levels 6 h postoperatively.

Although IL-6 is an integral mediator of the physiologic acute phase response to injury, excessive and prolonged post-injury elevations of circulating IL-6 concentrations are associated with mortality and morbidity. IL-6 has been the most consistently identified cytokine mediator of post-injury complications.[16] A greater degree of pain in the placebo group may have resulted in an increased stress response and thus increased plasma IL-6 concentration An increased use of morphine in this group may have had a direct effect in increasing IL-6, as morphine has been shown to promote the release of IL-6 from lipopolysaccharide stimulated monocytes.[17]

Our selection of sampling times was based on previous evidence that demonstrated that the postoperative increase in plasma IL-6 concentration begins at 2–4 h. Although IL-6 concentrations tended to increase to a lesser extent in group D at all postoperative time points, the difference was statistically significant at 6 h only. The limited extent of the IL-6 response (in both groups) at 24 and 48 h after the procedure may have decreased the likelihood of demonstrating an inhibitory effect of dexketoprofen.

In conclusion, dexketoprofen 25 mg tds, administered perioperatively as an adjuvant to opioids is a highly effective analgesic regimen in the treatment of pain after hip arthroplasty. In addition, this regimen appears to decrease the postoperative pro-inflammatory response.

Acknowledgement

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Randomized crossover comparison of the ProSeal with the classic laryngeal mask airway in unparalysed anaesthetized patients

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Background. The ProSeal is a wire-reinforced laryngeal mask airway with an additional drain tube that leads to the distal tip of the laryngeal cuff. The design should improve the seal with the larynx.

Methods. The ProSeal and classic laryngeal mask airways were compared in 180 patients in a randomized crossover study. Patients were anaesthetized without neuromuscular blocking drugs.

Results. The ProSeal took more time and more attempts to insert successfully than the classic laryngeal mask airway. Insertion was successful on the first attempt in 81% of cases with the ProSeal and 90% with the classic laryngeal mask airway. The ProSeal required more air to achieve an intracuff pressure of 60 cm H_2O (6 ml more for size 4 and 12 ml more for size 5). Laryngeal seal pressure was better with the ProSeal than the classic laryngeal mask airway. Median seal pressure was 29 cm H_2O with the ProSeal and 18 cm H_2O with the classic laryngeal mask airway. Laryngeal seal pressure was greater than 20 cm H_2O in 87% of patients with the ProSeal and 41% with the classic laryngeal mask airway. Laryngeal seal pressure was greater than 40 cm H_2O in 21% of patients with the ProSeal and in none of the patients with the classic laryngeal mask. Once placed, the ProSeal remained a stable and effective airway. Gastric tube insertion through the drain tube was attempted in 147 cases and was successful in 135 (92%).

Conclusion. The ProSeal is more difficult to insert than the classic laryngeal mask airway but allows positive pressure ventilation more reliably than the classic laryngeal mask airway.

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The ProSeal laryngeal mask airway (Intavent Orthofix, Maidenhead, UK) was described by Brain in 2001. The airway tube is wire-reinforced, like a flexible laryngeal mask airway. There is an additional drain tube placed laterally to the airway tube (Fig. 1). The drain tube passes through the mask part of the device and exits at the distal tip of the laryngeal cuff. This drain tube is designed to allow insertion of a gastric tube and to vent gas or liquid from the upper oesophagus. Venting of gas from the drain tube during assisted ventilation at normal pressures should indicate misplacement of the device. The laryngeal cuff of the ProSeal is made of softer silicone than that of the classic laryngeal mask airway and covers the posterior aspect of the bowl of the mask. When inflated, this cuff presses the bowl of the device forwards and is designed to improve the seal with the larynx. The bowl of the ProSeal is deeper than that of the classic laryngeal mask airway and it does not have aperture bars. The increased depth of the bowl is also designed to improve the seal with the larynx. The device has an integral bite block. The ProSeal may be inserted with a finger, like the classic laryngeal mask airway, or with an

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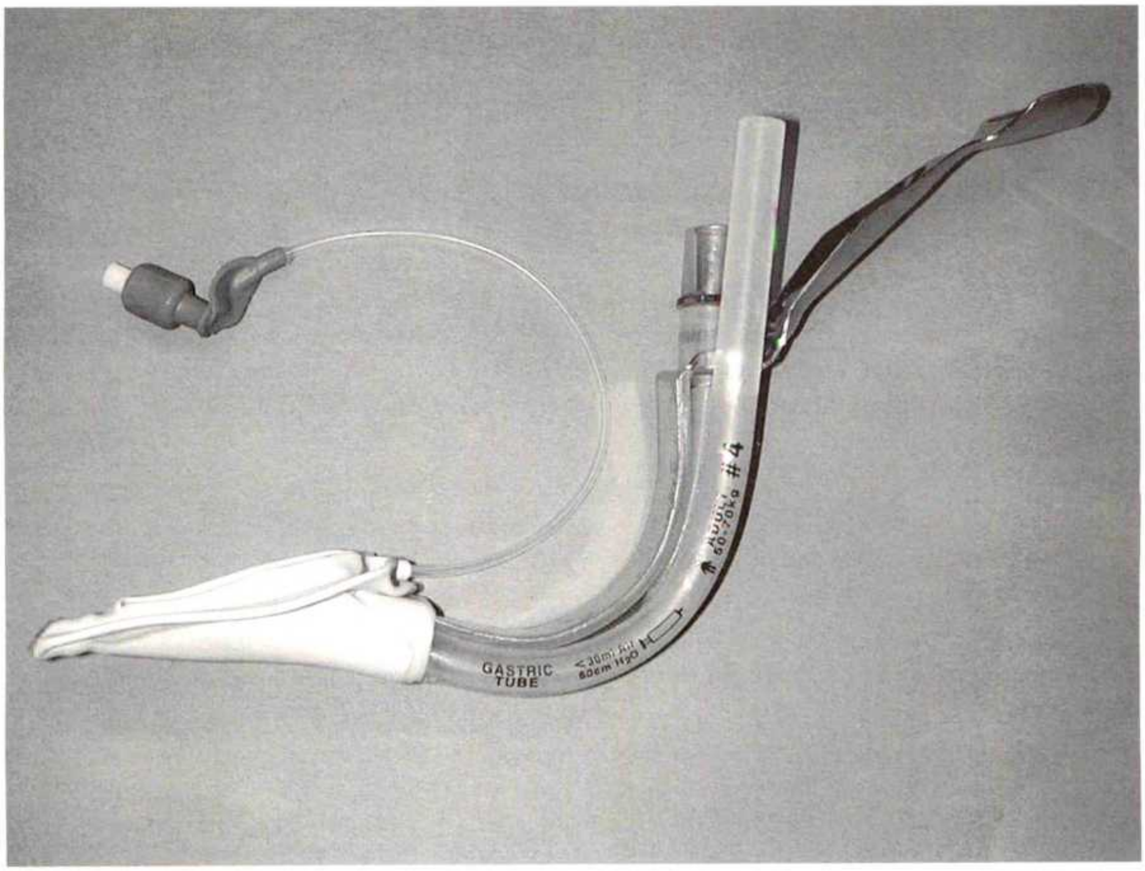

Fig 1 The ProSeal laryngeal mask airway.

insertion tool (Fig. 2). This tool seats in a locating strap at the anterior base of the laryngeal cuff and increases the rigidity of the device. With the introducer tool, the insertion technique is as for the intubating laryngeal mask airway and does not require a finger to be placed in the mouth. The technique using the introducer is recommended by the manufacturer.[2]

We assessed the ProSeal laryngeal mask airway and compared it with the classic laryngeal mask airway. We measured the seal with the larynx compared with the classic laryngeal mask airway for positive pressure ventilation and assessed the performance of the drain tube.

Method

We obtained the approval of the multicentre regional ethics committees. Informed written consent was obtained from all patients. Patients were studied with both a ProSeal and a classic laryngeal mask airway. The order in which these were used was randomized by the use of opaque sealed envelopes.

Premedication with oral temazepam 10–20 mg was used when indicated. Anaesthesia was induced with propofol and fentanyl 1–2 $\mu g\ kg^{-1}$ and maintained with either propofol infusion or a volatile anaesthetic in nitrous oxide and oxygen. Standard anaesthetic monitoring was used. The size of device to be used was decided by the individual investigator. Both devices were deflated fully before insertion. The ProSeal was inserted with either the ProSeal introducer tool or the index finger, as described in the manufacturer's product literature. The classic laryngeal mask was inserted with the standard technique [3]. A maximum of three attempts were allowed with each device. After insertion, the cuff was inflated with air to a pressure of 60 cm H_2O. A blob of lubrication gel was placed over the proximal opening of the ProSeal drain tube. Positive pressure ventilation was started at a tidal volume of 8 ml kg^{-1}. Adequacy of ventilation was assessed by chest movement, the capnograph signal and the presence or absence of an audible leak. With the ProSeal, the drain tube was also observed for displacement of the gel. Seal pressure was measured by stopping ventilation, occluding the spill valve with a fresh flow rate of 5 litre min^{-1} until airway pressure reached a steady value (seal pressure). The airway pressure was not allowed to exceed 40 cm H_2O. Seal pressure was observed and recorded by someone other than the investigator, to reduce observer bias. After measurement of seal pressure, intermittent positive pressure ventilation was restarted. The airway tube and drain tube were examined with a flexible fibreoptic scope. The view from the bulb of either device was graded in a standardized manner (Table 1). A single attempt was made to pass a

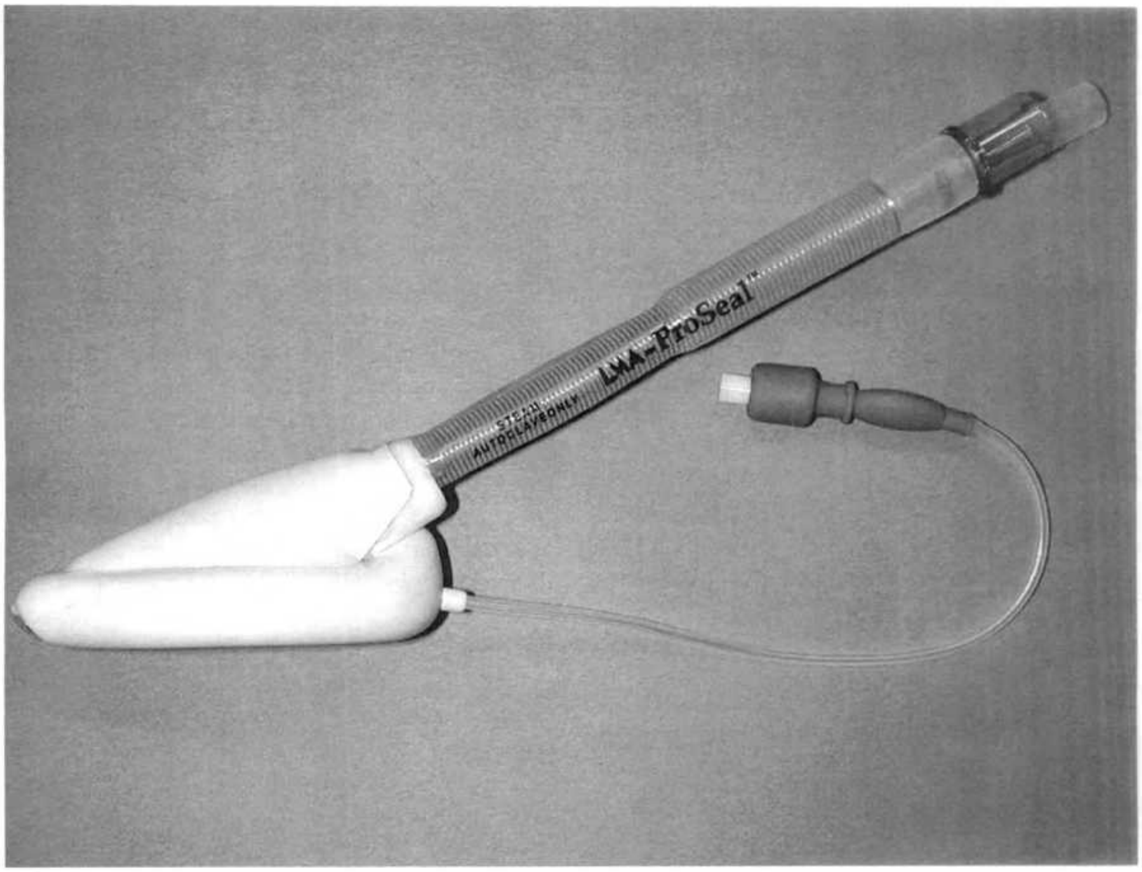

Fig 2 The ProSeal laryngeal mask airway mounted on its introducer.

gastric tube through the drain tube of the ProSeal. Placement of the gastric tube in the stomach was confirmed by aspiration of gastric contents or by auscultation over the stomach as air was syringed into the tube. The cuff was then deflated and the volume of air recorded. This completed the evaluation of the first device used, and it was removed. The same procedure was then followed for the other device. The second device was then used for the duration of the surgical procedure. At the end of the surgical procedure, anaesthesia was discontinued and the device was removed as the patient's reflexes returned, in accordance with the manufacturer's recommendations.[2 3] A checklist of complications relating to insertion, maintenance and removal was completed after use of each device.

Power analysis before the study suggested a sample size of 600 patients might be needed to detect a 3% difference in satisfactory ventilation with 80% power and a significance level of 0.05 (modified Lehr equation). Interim analysis of results was performed after each 100 patients and the study was stopped when these results showed clinically and statistically significant differences between the groups. Results were analysed using the statistical package Analyse-it and Microsoft Excel 97. Non-parametric tests were used where normal distribution was not clearly demonstrated. A P value of $\leqslant 0.05$ was taken to denote statistical significance.

Table 1 Classification of laryngeal view

Grade	Description of view
1	Clear view of vocal cords
2	Only arytenoids visible
3	Only epiglottis visible
4	No laryngeal structures visible

Results

One hundred and eighty patients were studied. Patient details are presented in Table 2 and full results are presented in Table 3. The ProSeal was used first on 92 and the classic laryngeal mask airway on 88 occasions. The ProSeal and classic laryngeal mask airway used were the same size for all patients except on one occasion. ProSeal insertion was with the introducer tool in 120 cases and without it in 60 cases. Insertion at the first attempt was less frequent with the ProSeal than with the classic laryngeal mask airway ($P<0.05$). The time required for insertion was longer with the ProSeal than for the classic laryngeal mask airway ($P<0.0001$). The time difference was 5 s (95% confidence interval 4–7). To achieve a cuff pressure of 60 cm H_2O, the ProSeal required significantly more air than the classic laryngeal mask airway. Size 4 masks required an extra 6 ml

(95% confidence interval 5–9) and size 5 masks an extra 12 ml (8–15). Airway maintenance was possible in all cases with the classic laryngeal mask airway and in all cases except two with the ProSeal. Positive pressure ventilation was entirely successful (satisfactory chest movement and capnography with no audible gas leak) in more patients using the ProSeal than with the classic laryngeal mask airway ($P<0.0001$). Seal pressure for the ProSeal was higher than for the classic laryngeal mask airway. The difference between the median seal pressures was 12 cm H_2O (95% confidence interval 11–13).

Gel placed on the end of the ProSeal drain tube was displaced during ventilation in 23 (13%) cases. In 12 of these cases, ventilation was otherwise assessed as entirely successful. Fibreoptic examination showed optimal positioning of the ProSeal in 125 (70%) and of the classic laryngeal mask airway in 131 cases (74%). Table 4 lists the grading of laryngeal view from the end of the ventilation tube. The differences in view achieved were not statistically significant. Fibreoptic examination in the patients in whom gel was displaced from the drain tube revealed a grade 1 view in 15 (65%) cases. Fibreoptic examination via the ProSeal drain tube was performed in 172 cases. This showed mucosa but no laryngeal structures in 170 (99%) cases. The oesophagus was seen to be patent in a few cases only. Gastric tube insertion was attempted in 147 and was successful in 135 (92%) cases.

Table 2 Patient details. M=male; F=female

Gender (M, F)	69, 105 (not recorded in six cases)
Age [yr; median (range)]	47 (16–86)
Weight [kg; median (range)]	70 (41–144)
ASA class [*n* (%)]	
1	130 (72)
2	46 (25)
3	4 (2)
Mallampati grade[27 28] [*n* (%)]	
1	72 (41)
2	73 (42)
3	28 (16)
4	2 (0.6)
Not recorded	5
Type of anaesthesia maintenance	
Volatile [*n* (%)]	58 (33)
Propofol infusion [*n* (%)]	119 (67)
Not recorded	3

Both devices were tolerated well and a clear airway was maintained throughout anaesthesia and emergence. There were few complications with either device. The commonest complication was the presence of blood on the device after removal. This occurred in 15 (9%) patients with the ProSeal and 11 (7%) patients with the classic laryngeal mask airway (Fisher's test, $P=0.54$). Other complications included two episodes of coughing, laryngospasm and breath-holding during ProSeal insertion. The number of complications occurring during use of the ProSeal was greater than with the classic laryngeal mask airway but the proportions of patients experiencing complications was not significantly different. Complications were generally minor with no sequelae. Complications are listed in Table 5. A total of nine (5%) patients complained of a sore throat in the recovery area.

Insertion using the introducer tool took 3 s longer (Table 6). Other differences between techniques were statistically significant but not clinically important.

The number of patients studied by individual investigators ranged from four to 61. The results from all investigators were in broad agreement, with the exception of one centre.

Two ProSeals failed during sterilization. The cuffs developed leaks where the posterior cuff was bonded to the stem of the device.

Table 3 Results of comparisons between the ProSeal and classic laryngeal mask airway

	ProSeal	Classic laryngeal mask airway	*P*	Statistical test
Attempts at insertion [*n* (%)]				
1	145 (81)	161 (90)		
2	25 (14)	14 (8)		
3	10 (5)	4 (2)	<0.05	χ^2
Successful insertion [*n* (%)]	178 (99)	180 (100)	0.5	Fisher's exact
Insertion time [s; median (range)]	15 (5–300)	10 (5–85)	<0.0001	Wilcoxon signed rank
Extra induction agent needed [*n* (%)]	10 (5)	16 (10)	0.232	Fisher's exact
Volume of air [ml; mean (SD)]				
Size 4	25 (6)	19 (6)	<0.0001	Paired *t*-test
Size 5	33 (11)	21 (8)	<0.0001	Paired *t*-test
Ventilation				
Chest rise [*n* (%)]	177 (98)	175 (97)	0.72	Fisher's exact
No audible leak [*n* (%)]	155 (86)	119 (66)	<0.0001	Fisher's exact
Gel dislodged from drain [*n* (%)]	23 (13)	–	–	–
Seal pressure [cm H_2O; median (interquartile range)]	29 (23–38)	18 (14–22)	<0.0001	Wilcoxon signed rank
Seal pressure $\geqslant$20 cm H_2O [*n* (%)]	155 (87)	73 (41)	<0.0001	Fisher's exact
Seal pressure $\geqslant$30 cm H_2O [*n* (%)]	87 (48)	8 (4)	<0.0001	Fisher's exact
Seal pressure $\geqslant$40 cm H_2O [*n* (%)]	38 (21)	0 (0)	<0.0001	Fisher's exact

Discussion

The ProSeal is a suitable device for positive pressure ventilation. Insertion was successful in 178 (99%) of the 180 patients within three attempts. Ventilation without audible leakage of gas was possible in 86% of the patients. Seal pressure was consistently greater than with the classic laryngeal mask airway and the difference was both statistically and clinically significant. The ProSeal provided a better seal than the classic laryngeal mask airway in 87% of patients. The ProSeal was positioned over the laryngeal inlet as accurately as the classic laryngeal mask airway and successful passage of a gastric tube via the oesophagus was usually achieved easily.

This study was done without the use of neuromuscular blocking drugs. Two sizes of device, 4 and 5, were used. We demonstrated that the median seal pressure with the ProSeal is 12 cm H_2O greater than with the classic laryngeal mask airway. Two smaller studies of seal pressure in paralysed patients used a size 4 ProSeal only. In one study of 30 patients, the difference in seal pressure was 14 cm H_2O,[1] while in the second study, with 60 patients, the difference was 10–12 cm H_2O.[4] Our results underestimate the true difference, as in 21% of cases the seal pressure achieved with the ProSeal exceeded the upper limit we set.

Table 4 Laryngeal view achieved [*n* (%)]

Grade	ProSeal (*n*=178)	Classic laryngeal mask airway (*n*=176)
1	125 (70)	131 (74)
2	30 (17)	28 (16)
3	19 (11)	14 (8)
4	4 (2)	3 (2)
χ^2 test *P*=0.77		

Table 5 Complications during use of the device. Fisher's test. **P*=0.06, ***P*=0.02

Complication	ProSeal [*n* (%)]	Classic laryngeal mask airway [*n* (%)]
Insertion		
Coughing	9 (5)	1 (0.6)
Laryngospasm	2 (1)	1 (0.6)
Breath-holding	1 (0.6)	0 (0)
Excessive movement	1 (0.6)	0 (0)
Blood on removal	16 (9)	11 (6)
Maintenance and removal		
Loss of airway	0 (0)	1 (0.6)
Troublesome secretions	1 (0.6)	0 (0)
Number of patients experiencing complications	26 (14)	14 (8)*
Total number of complications	30 (17)	14 (8)**

A limitation of the study is that anaesthetic technique was not standardized. However, all patients received the same anaesthetic with the exception of the use of propofol or isoflurane for maintenance of anaesthesia. ProSeal placement in patients who received volatile anaesthesia took 7 s longer than in those maintained with total intravenous anaesthesia, but the number of insertion attempts, failure rate and the number of complications did not differ significantly.

All investigators took longer to insert the ProSeal than the classic laryngeal mask airway but the absolute time difference was of negligible clinical importance. Investigators required more attempts to insert the ProSeal successfully. Complications were more frequent with the ProSeal but were minor and without sequelae. There was general agreement that the device is more difficult to place than the classic laryngeal mask airway. This applied whether the introducer tool or a finger was used for insertion. We found no clinically important differences in insertion characteristics whether or not the introducer was used. Previous work in paralysed patients has shown greater success with insertion when the introducer is used[5] but we did not find this. Insertion may be more difficult because the device is larger and bulkier than the classic laryngeal mask airway and more mouth opening is needed. During insertion of the ProSeal, there were more complications (including movement, coughing, breath-holding and laryngospasm) than with the classic laryngeal mask. A greater depth of anaesthesia may be needed for insertion of the ProSeal than the classic laryngeal mask airway, but this was not studied specifically. When deflated, the semirigid distal end of the drain tube forms the leading edge of the ProSeal, which is

Table 6 Comparison between insertion of the ProSeal with and without the introducer tool

	With introducer (*n*=60)	Without introducer (*n*=120)	Difference (95% CI)	*P* (statistical test)
Successful insertions (*n*)	60	118		0.89 (Fisher)
Insertion time (s, median)	18	15	3 (0 to 6)	0.02 (Mann–Whitney)
Extra propofol needed (*n*)	7	21		0.43 (Fisher)
Seal pressure (cm H_2O, median)	30	29	1 (4 to −2)	0.49 (Mann–Whitney)
Cuff volume (ml, median)	26	28	2 (−2 to −1)	0.02 (Fisher)
Position (*n*)				
1	43	83		
2	10	20		
3	5	13		
4	1	3		0.944 (χ^2)
Leak during ventilation (*n*)	5	23		0.07 (Fisher)

more rigid than the leading edge of the classic laryngeal mask airway. These factors may contribute to difficult insertion and minor trauma. All investigators were experienced anaesthetists and had inserted a minimum of five ProSeals before starting the trial. Despite this, several investigators needed fewer insertion attempts in the second half of the study than in the first. Whether this indicates that there is a long learning curve is unclear.

All study centres performed equally well, with one exception. In one centre, where fewer than 10% of all cases were studied, the use of the ProSeal (and the classic laryngeal mask airway) was considerably less successful than at the other four centres. Both failures with the ProSeal occurred at this centre and, in comparison with results from the other centres, both the ProSeal and the classic laryngeal mask airway were more frequently poorly placed. Seal pressures were significantly lower at this centre with both the ProSeal and the classic laryngeal mask airway. For both devices, the volume of air used for inflation was greater than at the other centres. Careful examination of these outlying results did not reveal an explanation. Minor differences in cuff inflation volume do not explain the findings.

The cuffs for all devices were inflated to a predetermined pressure (rather than a volume). The ProSeal cuff has a larger volume than that of the classic laryngeal mask airway *in vitro*.[1] Despite the larger static cuff volume, the difference in volume required to reach target pressure was small. Small increases in the volume of air caused marked increases in intra-cuff pressure. This might be explained by the ProSeal adapting more closely to the shape of the pharynx and larynx,[1] which might account for the improved seal pressure and low compliance during further inflation.

Two ProSeals failed in similar fashion. Manufacture of the back cuff is technically demanding. Unlike the cuff of the classic laryngeal mask airway, the ProSeal cuff cannot be made as a single piece of silicone. Silicone joins may lead to device weakness and scrupulous deflation of the device is necessary before sterilization. We did not encounter any device failures after adopting this precaution.

The drain tube appeared to be placed optimally in all but one case. Gastric tube insertion was remarkably easy in the majority of cases. On occasions when insertion was not possible, the drain tube appeared to have kinked in the posterior pharynx.

Use of a laryngeal mask airway for positive pressure ventilation is not new but is regarded by some as controversial. The ProSeal provides a more reliable airway than the classic laryngeal mask airway for positive pressure ventilation. The lungs of most healthy patients can be ventilated if the seal pressure exceeds 20 cm H_2O. In this study, the seal pressure was above this value in 87% of cases with the ProSeal and 41% with the classic laryngeal mask airway. If peak inflation pressure exceeds leak pressure, the likelihood of gastric insufflation is increased. In one study, leakage of inspired volume increased from 13% to 25% as peak pressure was increased from 15 to 30 cm H_2O.[4] Our results suggest that, if a classic laryngeal mask airway is selected for positive pressure ventilation, leakage will occur in more than half of the patients, but that leakage occurs in very few cases with the ProSeal.

The risk of aspiration with the classic laryngeal mask airway is probably low[5] [6] but remains controversial.[7] [8] The ProSeal drain tube allows easy passage of a gastric tube, which enables emptying of the stomach of gas or fluid. There is evidence from cadavers that the drain tube allows regurgitated fluid to bypass the larynx even when no gastric tube is in place.[10] Further study is needed to show that the ProSeal will reduce the risk of aspiration of regurgitated matter. Use of the classic laryngeal mask airway is an accepted technique for gynaecological laparoscopy[11] [12] and is currently used by up to 60% of UK anaesthetists for this procedure.[13] However, in the same study 89% of anaesthetists still intubated some patients and 35% intubated all patients. Seventeen per cent of laryngeal mask airway users expressed some concern with the technique. The classic laryngeal mask airway is used less widely for upper abdominal laparoscopic surgery, although several reports exist.[14] [15] Increased seal pressure and access to drain the stomach are distinct advantages of using the ProSeal for such procedures, but further evaluation is required.

Recent studies show that the classic laryngeal mask airway provides smooth and safe emergence from anaesthesia with less haemodynamic disturbance[16] and fewer respiratory complications[17] compared with emergence with a tracheal tube. For most patients and most operations, these considerations are not critical. However, patients emerging from anaesthesia for neurosurgery, cardiac surgery and open eye surgery benefit from a smooth recovery. The ProSeal may find a role during such procedures, either as the sole airway or as a secondary airway inserted at the end of surgery before lightening anaesthesia.

There are other potential roles for the ProSeal in the intensive care unit. The classic laryngeal mask airway has been used for short-term ventilatory support[18] [19] and for weaning from ventilation.[20] The ProSeal drain tube would allow insertion of a gastric tube to prevent gastric distension and facilitate enteral feeding (although regurgitation cannot be ruled out). The classic laryngeal mask airway is often used for airway maintenance during percutaneous tracheostomy.[21] [22] These patients have typically poor lung compliance and the improved laryngeal seal provided by the ProSeal would enable better ventilation during the procedure.

The classic laryngeal mask airway is widely used as a rescue airway in failed intubation.[23] In experienced hands, if lung compliance is reduced or the risk of aspiration is high, the ProSeal could allow more reliable positive pressure ventilation and the ability to drain the stomach, which might have become inflated during multiple attempts at bag-valve-mask ventilation.

Finally, the ProSeal has potential advantages over the classic laryngeal mask airway during cardiopulmonary resuscitation (CPR). The classic laryngeal mask airway is recommended for airway management during CPR in the current international guidelines.[24] The incidence of regurgitation during CPR when a classic laryngeal mask airway is used as the first airway adjunct is of the order of 3.5%.[25] This could be less with the ProSeal because the improved laryngeal seal should reduce the risk of gastric inflation and the drain tube provides an opportunity to empty the stomach. This supposition is entirely untested. Non-anaesthetists are able to place the classic laryngeal mask airway with considerable success[26] but the ProSeal is less easy. Further work is needed to determine whether infrequent users and non-anaesthetists are able to place the ProSeal with the same degree of accuracy before it can be recommended for use in resuscitation.

There might be a temptation to consider the ProSeal as a universal substitute for the tracheal tube. However, on a minority of occasions placement does not allow positive pressure ventilation. Concern about regurgitation also remains and we have not studied this. We have not compared the relative safeties of the ProSeal and the classic laryngeal mask airway. Further data from large studies or widespread clinical use will be needed before these questions can be answered.

In summary, we have shown that the ProSeal provides improved seal pressure for positive pressure ventilation compared with the classic laryngeal mask airway. It also provides an excellent route for insertion of a gastric tube. These benefits are at the cost of slightly increased difficulty in insertion of the ProSeal.

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The ProSeal laryngeal mask: results of a descriptive trial with experience of 300 cases[†]

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Background. The ProSeal laryngeal mask airway (PLMA) is a new laryngeal mask device with a modified cuff and a drainage tube.

Methods. We assessed the PLMA in 300 anaesthetized adults either paralysed or breathing spontaneously. We assessed insertion characteristics, airway seal pressures, haemodynamic response to insertion, ease of gastric tube placement, gastric insufflation, and postoperative sore throat.

Results. Insertion was successful in 294 patients (98%) and graded as easy in 274 patients (91%). We found no difference in ease of insertion or success rate with either the introducer or the finger insertion method, or in paralysed or non-paralysed patients. Mean airway seal pressure was 29 cm H_2O, and 59 patients (20%) had seal pressures greater than 40 cm H_2O. No gastric insufflation was detected. Gastric tube placement was successful in 290 of 294 patients (98.6%). There was no cardiovascular response to insertion, with a small reduction in heart rate 5 min after insertion and significant decreases in mean arterial pressure at 1 and 5 min after insertion. Sore throat was noted in 23% patients after operation and in 16% of patients after 24 h, with 90% of the sore throats described as mild.

Conclusions. The PLMA is a reliable airway management device that can give an effective glottic seal in paralysed and non-paralysed patients. The device allows the easy passage of a gastric tube, causes a minimal haemodynamic response to insertion, and an acceptable incidence of sore throat.

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The ProSeal laryngeal mask (PLMA; Intavent, Orthofix, Maidenhead, UK) is a new laryngeal mask device with a cuff modified to improve the seal around the glottis and a drainage tube to provide a bypass channel for regurgitated gastric contents, prevent gastric insufflation, and allow the passage of a gastric tube. These features are designed to improve the safety of the mask and broaden its scope, especially when used with positive pressure ventilation (Fig. 1).[1 2]

Two randomized crossover trials[1 2] compared the PLMA with the classic laryngeal mask (LMA[‡]) in anaesthetized, paralysed, adults. The PLMA was as easy to insert as the LMA when the introducer tool was used and the airway sealing pressure was 8–11 cm H_2O greater. Gastric tube placement was successful in all the patients. In both trials only size 4 masks were used.

We set out to assess the performance of sizes 4 and 5 PLMA in 300 anaesthetized adults, either paralysed or breathing spontaneously.

Methods

We studied 300 ASA I–III adult patients over 5 month periods. Research and ethical committee approval was obtained and all patients gave informed written consent. We studied patients undergoing routine elective surgery where a classic LMA would normally be used. Patients were

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[†] *Declaration of interest* Marland Medical South Africa funded the salary of a research assistant and provided the masks. AstraZeneca (South Africa) provided the propofol used for this study.

[‡] LMA® is the property of Intavent Limited.

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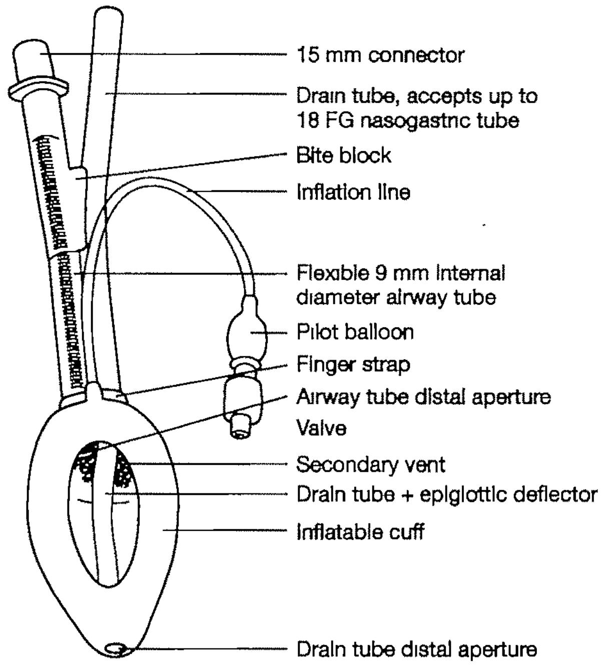
15 mm connector
Drain tube, accepts up to 18 FG nasogastric tube
Bite block
Inflation line
Flexible 9 mm internal diameter airway tube
Pilot balloon
Finger strap
Airway tube distal aperture
Valve
Secondary vent
Drain tube + epiglottic deflector
Inflatable cuff
Drain tube distal aperture

Fig 1 The ProSeal laryngeal mask seen from the front.[1]

excluded if they were at risk of aspiration. There were eight investigators who were consultants and senior registrars all of whom had more than 5 yr anaesthetic experience and had been trained to insert the PLMA as directed by the manufacturer. They carried out 10 insertions on a model and 10 insertions in patients before commencing the trial. Premedication consisted of oral temazepam 10 or 20 mg depending on body weight 1–2 h before surgery. Standard monitoring was applied before induction of anaesthesia. Anaesthesia was induced with fentanyl 1 µg kg^{-1} followed 2 min later by propofol 2–3 mg kg^{-1} until the eyelash reflex was abolished. In spontaneously breathing patients the PLMA was inserted immediately after this, when adequate jaw relaxation had been achieved. In patients to be paralysed and ventilated, an appropriate dose of a non-depolarizing agent was given and the PLMA inserted 2–3 min later. The decision to use neuromuscular blocking drugs depended on the surgical requirement for muscular relaxation. Anaesthesia was maintained with isoflurane and 66% nitrous oxide in oxygen using a circle absorber system. With the patient supine and the head in the neutral position resting on a pillow 7 cm in height, a PLMA (size 4 in females and size 5 in males) was inserted using either the index finger or the introducer tool. At the discretion of the investigator, a size 5 PLMA could be used in females taller than 165 cm or weighing more than 70 kg; in males less than 70 kg or shorter than 165 cm, a size 4 PLMA could be used. The index finger insertion method was identical to that recommended by the manufacturer for the classic LMA,[3] and the insertion method with the introducer tool was that described for the intubating laryngeal mask.[4] The cuff was inflated to obtain an intracuff pressure of 60 cm H_2O, measured with a calibrated aneroid manometer (Carron Medical® Control instruments RSA). The volume of air required was noted. The intracuff pressure was maintained at this pressure throughout the procedure. Arterial pressure (systolic, diastolic, and mean) and heart rate were recorded before induction, and at 1 and 5 min after insertion. After insertion and cuff inflation, manual ventilation of the lungs was carried out with the circuit closed to determine (i) whether an expired volume of more than 8 ml kg^{-1} could be achieved and (ii) whether leak occurred up the drainage tube when airway pressure was less than 20 cm H_2O. This pressure was chosen as leaks with a pressure less than 20 cm H_2O suggest malposition of the device.[1] Leak was detected by placing a 1 ml bolus of lubricant jelly in the proximal orifice of the drainage tube to seal it. The airway pressure at which this bolus was ejected was noted. If a leak occurred with an airway pressure less than 20 cm H_2O, malposition was assumed and the mask repositioned or reinserted. The number of insertion attempts required to achieve these criteria were recorded—a failed insertion attempt was defined as removal of the device from the mouth. Three insertion attempts were allowed before a failure of insertion was recorded. If the PLMA could not achieve a satisfactory airway within three insertions either a classic LMA was inserted or the trachea was intubated conventionally. A satisfactory placement was noted if the expired tidal volume was more than 8 ml kg^{-1} and there was no drainage tube leak. Once a satisfactory placement had been achieved, the PLMA was fixed in place by taping the tube over the chin. Ease of insertion was noted. An easy insertion was defined as insertion within the pharynx without resistance in a single manoeuvre. A difficult insertion was one in which there was resistance to insertion or where more than one manoeuvre was required to seat the device within the pharynx.

The airway sealing pressure was then determined as described previously[5] by closing the expiratory valve of the breathing system. With a fresh gas flow rate set to 3 litre min^{-1} the pressure in the circuit was allowed to increase until no further increase in pressure occurred. The airway pressure was not allowed to exceed 40 cm H_2O. The location of gas leak when the pressure became stable was determined as mouth (audible), stomach (epigastric auscultation), or drainage tube (bubbling of lubricant).

In 102 patients, a fibre optic bronchoscope (Olympus BF 240®) was passed down the airway to a position 1 cm proximal to the end of the tube and the view graded using an established scoring system:[6] 4=only vocal cords visible; 3=vocal cords and posterior epiglottis visible; 2=vocal cords and anterior epiglottis visible; 1=vocal cords not seen.

A lubricated size 16 or 18 French gauge gastric tube was inserted down the drainage tube. Gastric contents were aspirated with a 50 ml catheter tipped syringe; the volume measure and the pH were tested with litmus paper. The gastric tube was left *in situ* for the duration of the procedure and the total volume drained noted. The tube was removed at the end of the procedure while the patient was still

Table 1 Patient characteristics

	Mean (SD)	Range
Age (yr)	41 (14)	18–85
Height (cm)	168 (11)	117–210
Weight (kg)	70 (14)	45–120
BMI (kg cm^{-2})	25 (5)	16–41
Dose propofol (mg)	161 (38)	70–300
Duration of surgery (min)	65 (43)	10–240

anaesthetized. The duration of the surgery was noted. Once the patient was awake the mask was removed and the pH of the back and front of the mask tested by litmus paper sensitive to changes of 1 pH unit from pH 1 through to 10. (Duotest® Macherey-Nagel Duren, Germany). The patients were asked in the recovery room and 24 h later whether they had a sore throat. If a positive answer was obtained, they were asked to grade the sore throat as mild, moderate, or severe.

Statistics

For statistical analysis, we used Statistica for Windows® program running on an IBM compatible machine under Windows 98. Categorical data were analysed with Fisher's exact test for two comparisons, or the chi-squared test for more categories, with Yates correction where appropriate. Quantitative data were analysed after exclusion of upper limits (e.g. maximum seal pressure) where appropriate by analysis of variance with post-hoc testing using 95% confidence intervals. We compared seal pressures between males and females and between paralysed and non-paralysed patients, and the method of insertion. These comparisons were not of randomly allocated groups and were not primary end-points of the study design. The analysis was to allow the development of hypotheses for future testing.

Results

The characteristics of the 300 patients and details of anaesthesia are shown in Tables 1 and 2. Insertion was successful in 294 patients (98%), required one attempt in 243 patients (81%), and was graded as easy in 274 patients (91%) (Table 3). Of the six failed insertions, insertion of a classic LMA was possible in two patients but unsuccessful in two others, while in the other two failures, classic LMA insertion was not attempted and the trachea intubated conventionally. Table 4 lists the insertion failures by investigator and technique. The individual choices among investigators for the use of the introducer or finger insertion technique are shown in Table 5. There did not seem to be a difference in ease of insertion or success rate using either the introducer or the finger technique, or in paralysed *vs* non-paralysed patients (Table 6). However, as neither the insertion technique nor the use of neuromuscular blocking drugs was randomized, no firm conclusions can be drawn.

Table 2 Details of anaesthesia

		Number
Gender	Male	133
	Female	167
ASA status	I	188
	II	86
	III	18
Neuromuscular block	Yes	117
	No	183
Size of mask	4	167
	5	133
Mode of insertion	Finger	122
	Introducer	172
Position of patient	Supine	191
	Lithotomy	61
	Trendellenberg	36
	Sitting	8
	Lateral	2

Table 3 Ease of ProSeal insertion

	Number	
	n=300	%
One attempt	243	81
Two attempts	45	15
Three attempts	6	2
Failed	6	2
Easy	274	91
Difficult	20	7

Table 4 Failed placements

Investigator number	Paralysed	Mode of insertion
1	Yes	Introducer
1	Yes	Introducer
2	No	Introducer
7	No	Introducer
7	No	Introducer
8	No	Finger

Table 5 Numbers of insertions for each investigator

Investigator number	Finger insertion	Introducer insertion
1	44	68
2	23	35
3	13	8
4	10	5
5	17	13
6	3	32
7	2	10
8	11	6
Total	123	177

Power analysis using our data shows that a sample size of approximately 500 randomized subjects would be needed to compare the insertion techniques.

The mean (range) volume of air required to achieve an intracuff pressure of 60 cm H_2O was 28 (14–45) ml for the size 4 mask and 37 (18–63) ml for the size 5 mask. Airway

Table 6 Characteristics of insertion

	Finger		Introducer		Paralysed		Non-paralysed	
	n=122	%	n=172	%	n=117	%	n=183	%
One attempt	97	80	146	85	93	80	150	82
Two attempts	21	17	24	14	19	16	26	14
Three attempts	4	3	2	1	3	3	3	2
Easy	109	89	165	96	107	91	167	91
Difficult	13	11	7	4	8	7	12	7

Table 7 Airway seal pressures

	n	No. with seal >40 cm H_2O	P	No with seal <40 cm H_2O	Mean (SD) cm H_2O	P
Total sample	294	59		235	29 (5.9)	
Females	165	42	<0.05	123	30 (5.5)	<0.05
Males	129	17		112	28 (6.3)	
Paralysed	115	27	0.3	85	30.3 (5.9)	<0.001
Non-paralysed	179	32		147	28.3 (5.9)	

seal pressures are shown in Table 7. Where a size 4 PLMA was used in males (16 patients), seal pressure was similar to that of the whole group (29.5 cm H_2O) and when a size 5 PLMA was used in females (16 patients) seal pressure was slightly higher (34.9 cm H_2O). Significantly more females than males achieved a seal pressure of 40 cm H_2O or greater (P=0.012). In those whose seal pressures were less than 40 cm H_2O, the seal pressure was statistically significantly greater in females than in males (P=0.05) but this difference was not clinically important. There were no differences in the number of patients achieving seal pressures greater than/equal to 40 cm H_2O between those paralysed and not paralysed; there was a statistically significant (P=0.01) but clinically unimportant difference in seal pressure in those whose seal pressure was less than 40 cm H_2O. Gas leakage at airway sealing pressure was from the mouth in 290 cases (98.2%) and from the drainage tube in four patients (1%). Gastric insufflation was not detected in any patient. In the patients studied with the fibre optic bronchoscope the view ratings were four in 47 cases, three in 31 cases, two in 16, and one in eight. Vocal cords were seen in 94 of 102 patients (92%). Gastric tube placement was successful in 290 patients (97%), graded as easy in 286 of these patients (98%), and difficult in four. Gastric tube placement failed in four patients. Fluid was aspirated from the gastric tube initially in 193 patients (67%) and in 225 patients (76%) by the end of the procedure, with a mean (range) initial volume of 20 (0–120) ml and a final volume of 24 (0–180) ml.

Haemodynamic measurements were incomplete in 32 patients and these values were not analysed. Complete haemodynamic data were available for 268 patients. Mean heart rate did not change at 1 min after insertion and decreased to 78 beats min^{-1} at 5 min after insertion (P=0.13) (Fig. 2). There was a significant decrease in mean arterial pressure at 1 min after insertion compared with before induction (77 *vs* 102 mm Hg, P<0.001) and at 5 min after insertion compared with the values after 1 min (71 *vs* 77 mm Hg, P=0.01) (Fig. 3).

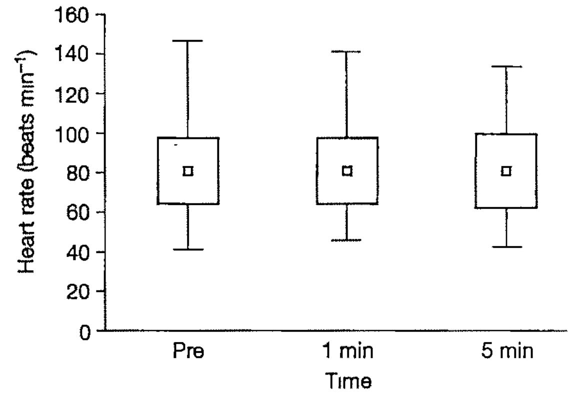

Fig 2 Heart rate response to PLMA insertion Mean with SD shown as boxes and range shown by whiskers Pre heart rate before induction; 1 min heart rate 1 min after insertion of PLMA, 5 min· heart rate 5 min after insertion of PLMA.

Litmus paper showed a pH less than 6 in one patient only, who tested pH 4 on the back of the mask only. Sore throat was reported by 60 of the 265 (23%) patients in the recovery room, 54 of whom (90%) described the sore throat as mild and six (10%) described it as moderate. The following day 41 out of 255 (16%) patients had a sore throat; 38 patients (92%) described the sore throat as mild and three (8%) described it as moderate. There were no reports of a severe sore throat.

Discussion

We studied the PLMA in 300 adult patients and found the following.

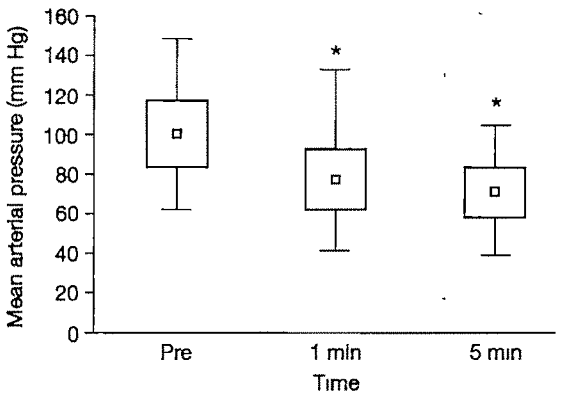

Fig 3 Mean arterial pressure response to PLMA insertion. Mean with SD shown as boxes and range shown by whiskers. Pre mean arterial pressure before induction, 1 min mean arterial pressure 1 min after insertion of PLMA; 5 min: mean arterial pressure 5 min after insertion of PLMA. *$P<0.01$ from previous value.

1. The PLMA was easy to insert with a high success rate.
2. There was no apparent difference in ease of insertion or success rate using either the introducer or the finger insertion method, or in paralysed compared with non-paralysed patients.
3. Mean airway sealing pressure was 10–12 cm H_2O higher than the airway seal pressure of 17–19 cm H_2O described for a classic LMA.[5,7,13]
4. No gastric insufflation was detected.
5. Gastric tube placement was successful in most patients (98.6%).
6. There was minimal haemodynamic response to insertion.
7. About 20% of patients had a mild sore throat.

The two small previous trials on the PLMA showed successful mask insertion and gastric tube placement in all patients, with airway sealing pressures 8–11 cm H_2O greater than the classic LMA.[1,2] We confirm in a larger study that the PLMA is a reliable airway device with a better glottic seal than the classic LMA, and that it allows the reliable placement of a gastric tube. The volume of the larger posterior cuff can make mask insertion difficult, with an insertion success rate of 92%.[8] This may have played a role in the failures of mask insertion that occurred in our trial, although our overall success rate of 98% is similar to the rates of 96–99.8% described previously for the classic LMA.[9,10] Brimacombe[2] reported that the introducer makes insertion easier. Some investigators preferred the introducer technique, but no apparent difference in ease of insertion or success rate to the finger insertion method was found in the sample as a whole. Neuromuscular block confers no advantage over propofol alone in providing optimum conditions for classic LMA insertion[11] and this seems to be the same for the PLMA. Neuromuscular block does not affect the directly measured mucosal pressures exerted by a classic LMA.[12] We found similar airway seal characteristics and performance in paralysed *vs* non-paralysed patients for the PLMA, but we did not do a randomized study. Greater seal pressures for females have been found previously for the PLMA[2] where size 4 masks were used for both females and males. Using predominantly a size 4 in females and a size 5 in males as recommended previously,[13] we found marginally greater seal pressures in females. A size 6 PLMA may be useful in tall men in whom a size 5 may be too small to achieve an adequate seal. Our failure to detect gastric insufflation agrees with the findings of Brimacombe,[2] although the sensitivity of epigastric auscultation has been questioned.[14] We observed that auscultation using an epigastric microphone is still required. Fibre optic view showed epiglottic down folding on occasions, possibly related to the larger proximal cuff bringing the epiglottis down during insertion. Failure of gastric tube placement can occur if the tip of the mask folds during insertion, so that the distal orifice of the drainage tube is occluded. This can occur if the mask is inserted at an acute angle to the oropharynx allowing the tip of the mask to fold against the posterior oropharyngeal wall before passing into the hypopharynx, and is more likely during light anaesthesia when muscle tone is greater. Insertion of the classic LMA causes a 0–20% increase in heart rate and mean arterial pressure,[15] which is less than laryngoscopy.[16,17] The larger size of the PLMA and the rigid introducer could cause a greater haemodynamic response. A recent report found the rigid intubating laryngeal mask produced a similar haemodynamic response to laryngoscopy.[18] We found that the PLMA caused no detectable response to insertion during propofol anaesthesia, with the heart rate and mean arterial pressure decreasing after insertion.

No regurgitation of gastric contents into the mask was found using the litmus paper technique. A single test at the end of the procedure may not be a sensitive way to detect this and further study with continuous measurement by pH probes down the drainage tube and into the bowl of the mask would be interesting. The incidence of sore throat after classic LMA insertion varies from 5.8–34%.[19] Brimacombe[20] recently showed that there was no difference between the PLMA and the LMA in directly measured mucosal pressures, so postoperative pharyngolaryngeal morbidity may be similar between the two devices. The incidence of sore throat in this trial supports a recent study on postoperative laryngopharyngeal morbidity with the classic LMA using low cuff volumes.[21] In conclusion, the PLMA is a reliable airway capable of achieving an improved seal with the glottis and allowing the passage of a gastric tube in both paralysed and non-paralysed patients, with minimal haemodynamic response to insertion and a similar incidence of sore throat to the classic LMA.

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BJA

LABORATORY INVESTIGATIONS

Increased airway resistance during xenon anaesthesia in pigs is attributed to physical properties of the gas

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Background. In this study we investigated the effects of the physical properties of xenon on respiratory mechanisms in pigs.

Methods. With institutional approval, 10 female pigs (mean 25.2 (SD 2.5) kg) were anaesthetized with thiopental, remifentanil, and pancuronium. Gas flow and pressure were recorded continuously at the proximal end of the tracheal tube during constant flow ventilation for control, with 100% oxygen (control), followed by 1.5% isoflurane in 70/30% nitrogen/oxygen, 1.0% isoflurane in 70/30% nitrous oxide/oxygen, and 70/30% xenon/oxygen in random order. Compliance (*C*) and resistance (*R*) were calculated using a single compartment model. Resistance was corrected for gas viscosities η and also for densities ρ and viscosities η as $(\rho^{*}\eta)^{1/2}$ to compare assumptions of laminar and mixed flow in the airways.

Results. With constant flow ventilation, xenon increases inspiratory pressure compared with other gas mixtures. There were no significant differences in resistance, corrected for laminar or mixed flow, between the gas mixtures. Xenon anaesthesia did not affect compliance.

Conclusions. The increase in airway pressure observed with xenon anaesthesia is attributed completely to its higher density and viscosity. Therefore, determination of airway resistance must take into account the physical properties of the gas. Xenon does not exert any major effect on airway diameter.

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At ambient temperature, pressure, and when water saturated, the density (ρ) and viscosity (η) of xenon is 5.44 g litre^{-1} and 2.25 10^{-5} Pa s^{-1}, respectively.[1] These values are substantially higher than those of the other gases used in anaesthesia and may affect the determination of respiratory mechanics. An increase in airway resistance during xenon anaesthesia has been reported in previous investigations, for example in pigs[2] and in open-chest dogs.[3] The question 'is this attributable to physical properties of the gas or if xenon affects airway resistance as such?' is yet to be answered.

When flow is laminar, viscosity is the only physical property of the inspired gas that has an influence on flow resistance. However, if flow is turbulent, resistance depends more on the density of the gas than its viscosity. The aim of this experimental study was to compare respiratory mechanics corrected for physical gas properties during xenon/oxygen anaesthesia to those with nitrogen/oxygen or nitrous oxide/oxygen, both with isoflurane, as the most frequently used inhaled anaesthetic. Two different, simplified assumptions of flow patterns, that are laminar, and mixed laminar and turbulent flow, were compared to determine if xenon affected airway resistance by a mechanism other than its physical properties.

Methods

The study was approved by the local Animal Care Committee as well as the governmental Animal Care Office and it was performed with 10 female German landrace pigs weighing 22–30 kg (mean 25.2 (SD 2.5) kg). Upon

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Table 1 Densities (ρ) and viscosities (η) at ambient temperature (20°C), pressure, and water saturated for various gas mixtures as used in this study

	O_2 100%	N_2/O_2 70/30%	N_2O/O_2 70/30%	Xenon/O_2 70/30%
ρ (g litre^{-1})	1.32	1.21	1.67	4.20
η (10^{-5} Pa s^{-1})	2.00	1.81	1.61	2.18

admission to the local institute for animal studies, the animals were thoroughly examined by a veterinarian. This examination included behaviour, motor ability, skin, hair, and cardiopulmonary auscultation. None of the animals showed any symptoms of disease and body temperature was between 38.1 and 39.2°C (mean 38.6). The animals were included in the study only after 5 days of appropriate feeding and observation without any abnormal findings.

Animal preparation

Animals received azaperone 4 mg kg^{-1} and ketamine 10 mg kg^{-1} intramuscularly for premedication, which was followed by cannulation of an ear vein. Continuous infusion of Ringer's solution 0.1 ml kg^{-1} min^{-1} was started, and general anaesthesia was induced by administration of thiopental 4 mg kg^{-1}, continuous infusion of remifentanil 0.25 µg kg^{-1} min^{-1}, and pancuronium 0.1 mg kg^{-1} followed by an infusion of 0.1 mg kg^{-1} h^{-1}. Orotracheal intubation was performed using a cuffed 5.0 mm ID tube (Mallinckrodt Medical, Athlone, Ireland) in four of the animals and percutaneous tracheotomy (because of difficulties on orotracheal intubation) using a 7.0 mm ID cannula (Ruesch Medical, Kernen, Germany) in six animals. Volume-controlled ventilation, using a closed circuit PhysioFlex anaesthesia ventilator (Draeger, Luebeck, Germany) was started using a tidal volume of 10 ml kg^{-1} with an inspiration:expiration ratio of 1:2, and a fixed ventilatory frequency of 24 breaths min^{-1} to maintain an end-tidal $P\text{CO}_2$ of 4.7–5.3 kPa. With this mode, the machine delivers a constant inspiratory flow (after a short period of exponential increase) by constantly moving the membrane of a membrane chamber within the circuit towards its outlet. The volume administered is measured by electronic detection of the membrane movement with an error of less than 10%. Thereby, the ventilator generates a ramp-like pressure. The ventilation pattern was kept constant throughout the experiment, which lasted 6–8 h.

Monitoring

With general anaesthesia, a 20-gauge Teflon cannula was inserted in a femoral artery, a pulmonary artery catheter was placed via a femoral vein, and the urinary bladder was catheterized. ECG, ear pulse oximetry, and systemic and pulmonary arterial pressure were monitored by a Datex AS/3 anaesthesia monitor (Datex-Engstrom, Helsinki, Finland). Gas concentrations were monitored using thermo-conductive analysis for xenon and infrared spectroscopy for the others (including end-tidal carbon dioxide) by the PhysioFlex machine. Pressure and flow were recorded at the proximal end of the tracheal tube using a CP-100 Pulmonary Monitor (Bicore, Irvine, CA, USA) from which raw data were exported on-line to a PC for further processing. The CP-100 uses a variable orifice flow meter for which single-use flow probes, calibrated for air, were supplied by the manufacturer. A new calibrated flow probe was used for each animal, and the tidal volume was calculated by integration of the flow–time curve. As demonstrated recently by Goto and colleagues,[4] readings of an orifice flow meter are dependent of gas composition. To allow for correction, tidal volume measured by the PhysioFlex ventilator, which is independent of gas composition, was divided by the value obtained from the CP-100 flow–time curve. This procedure revealed over-estimation of tidal volume by the CP-100 by 1.18 for oxygen, 1.09 for nitrogen/oxygen, 1.06 for nitrous oxide/oxygen, and 1.37 for xenon/oxygen. Thus, these factors were used for correction.

Determination of respiratory mechanics

Resistance (R) and compliance (C) were calculated according to the method published by Bates and co-workers using a single compartment model described by the equation:

$$V(t) \, / \, C + V'(t) \times R = a \; t$$

where $V(t)$ is volume, $V'(t)$ is flow, C is compliance, R is resistance, a is the slope of the inspiratory pressure increase for a ramp-like pressure as applied by the ventilator during inspiration, and t is time. From the recorded flow data, a flow–time curve is obtained from which instantaneous volume (V) is calculated. This is plotted against inspiratory time (T_I) which is consequently replaced by applied pressure according to $P(t) = a\ t$. The applied pressure is the sum of the pressure to overcome flow resistance ($P_{res}(t) = V'(t) \times R$) and the pressure to overcome elastic recoil forces ($P_{el}(t) = V(t)/C$). C is then derived from the linear part of the volume–time curve where flow is constant with $V' = a \times C$, and R equals the point of the time axis intercept derived from back-extrapolating this linear portion (called the time constant τ of the system), divided by the compliance.[5]

If the flow is fully laminar, P_{res} is proportional to the viscosity, η, while in turbulent flow it is mainly the density, ρ, which determines pressure when all other parameters are held constant. In physiological conditions, laminar flow is

Table 2 Schedules with different orders of the three parts of the study to which the animals were randomly allocated. Four animals received schedule I, and three had schedules II and III, respectively

Control	Experiments	Part I	Part II	Part III
100% O$_2$	Schedule I	Isoflurane/N$_2$/O$_2$ (1.5% in 70/30%)	Xenon/O$_2$ (70/30%)	Isoflurane/N$_2$O/O$_2$ (1.0% in 70/30%)
	Schedule II	Xenon/O$_2$	Isoflurane/N$_2$O/O$_2$	Isoflurane/N$_2$/O$_2$
	Schedule III	Isoflurane/N$_2$O/O$_2$	Isoflurane/N$_2$/O$_2$	Xenon/O$_2$

Table 3 Respiratory parameters median (first line) and interquartile range (second line) for each gas mixture (CON, control with O$_2$ 100%; N$_2$/O$_2$, isoflurane in N$_2$/O$_2$ 70/30%, N$_2$O/O$_2$, isoflurane in N$_2$O/O$_2$ 70/30%, XEN/O$_2$, xenon/O$_2$ 70/30%). V_t, tidal volume calculated from flow data as control of preset value, P_{peak}, peak inspiratory pressure, R_{uncorr}, calculated, uncorrected resistance, *C*, compliance. Upper part: end-expiratory pressure 0 (ZEEP), lower part: end-expiratory pressure 10 hPa (PEEP)

	CON	N$_2$/O$_2$	N$_2$O/O$_2$	XEN/O$_2$
ZEEP				
V_t (ml)	256	258	259	264
	(241–262)	(235–268)	(249–273)	(239–275)
P_{peak} (hPa)	20.2	17.9	19.1	22.1
	(17.2–22.8)	(16.0–20.3)	(16.5–21.1)	(17.0–30.0)
R_{uncorr} (hPa s^{-1} litre^{-1})	18.4	17.1	23.1	27.0
	(11.5–21.7)	(12.4–22.8)	(14.5–27.7)	(21.9–37.7)
C (ml hPa^{-2})	20.5	22.7	25.0	22.6
	(18.7–23.2)	(20.0–24.3)	(19.1–28.2)	(18.6–30.0)
PEEP				
V_t (ml)	258	257	251	261
	(230–265)	(240–266)	(246–268)	(232–267)
P_{peak} (hPa)	26.5	28.2	26.9	31.8
	(23.5–29.0)	(27.3–32.4)	(25.7–31.7)	(26.6–38.7)
R_{uncorr} (hPa s^{-1} litre^{-1})	15.7	17.4	17.7	28.6
	(10.7–20.6)	(11.7–18.2)	(14.4–25.0)	(22.5–34.7)
C (ml hPa^{-1})	24.2	21.3	26.0	22.1
	(22.1–28.8)	(18.8–24.7)	(19.0–30.2)	(18.6–26.4)

present in lower porcine as well as in human airways.[6] In a tracheal tube, there is a considerable amount of turbulence caused by tube connectors and the increase in diameter at the tip of the tube within the trachea and, thus, gas density must be taken into account. Pedley and colleagues[7] have suggested that the resistance ratio of two gas mixtures equals the ratio of their $(\rho*\eta)^{1/2}$ under physiological mixed flow conditions. The viscosities, η, and the densities, ρ, for 100% oxygen, 70/30% nitrogen/oxygen, 70/30% nitrous oxide/oxygen, and 70/30% xenon/oxygen are shown in Table 1. Viscosities and the terms $(\rho*\eta)^{1/2}$ were obtained and then normalized for those of 70/30% nitrogen/oxygen for better comparison. For example, the viscosity of xenon/oxygen (2.18×10^{-5} Pa s^{-1}) was divided by that of nitrogen/oxygen (1.81×10^{-5} Pa s^{-1}) to obtain a normalized η of 1.20 for xenon/oxygen. The results were compared with the ratios of the calculated, uncorrected resistances (R_{uncorr}) with the three gas mixtures to that with 70/30% nitrogen/oxygen to compare the assumptions on airway flow. Corrected resistance for laminar flow (R_{corrl}) was obtained by dividing R_{uncorr} by normalized η, and likewise, correction for mixed flow (R_{corrm}) was achieved by dividing R_{uncorr} by normalized $(\rho*\eta)^{1/2}$.

Study procedure

While anaesthesia was maintained with thiopental, remifentanil, and pancuronium, control data (CON) during ventilation with oxygen 100% were collected. Afterwards, only remifentanil and pancuronium were continued and the animals received anaesthetic gas mixtures of 1.5% isoflurane in 70/30% nitrogen oxygen, 1.0% isoflurane in 70/30% nitrous oxide oxygen, or 70/30% xenon oxygen according to one of three different schedules to which they were randomly allocated (see Table 2). After each experimental mixture, gas washout was performed with 100% oxygen and after the next gas concentrations had been reached, 20 min were allowed for equilibration before data collection. As positive end-expiratory pressure (PEEP) is often used in clinical routine to maintain compliance by preventing partial collapse of alveoli during mechanical ventilation, each part of the experiment was repeated with PEEP set to 10 hPa (10 cm H$_2$O). Zero end-expiratory pressure (ZEEP) and PEEP were performed in random order for each gas.

Data collection

When steady-state anaesthesia was established, pressure and flow data were collected as the mean values of three recordings during a 5-min period (taken at 0, 2.5, and 5 min) for each of the gas mixtures. From these recordings, compliance (*C*) and resistance (*R*) were calculated as described above.

Table 4 Uncorrected resistance (R_{uncorr}) at ZEEP (zero EEP) and PEEP (10 hPa EEP) and comparison of resistance ratios with viscosity ratios and $(\rho^*\eta)^{1/2}$ ratios. Ratios were obtained by dividing R_{uncorr}, η, and $(\rho^*\eta)^{1/2}$ of each gas mixture by the respective values for N_2/O_2. Note that resistance ratios are usually the underestimated by η ratios and closer to, although sometimes overestimated by $(\rho^*\eta)^{1/2}$ ratios as suggested by Pedley and colleagues[7]. Corrected resistance (R_{corrl} assuming laminar flow) is obtained by dividing R_{uncorr} by the respective η ratio. Likewise, R_{corrm} (assuming mixed flow) is obtained by dividing R_{uncorr} by the respective $(\rho^*\eta)^{1/2}$ ratio. Median values (interquartile range) from $n=10$

	R_{uncorr} (hPa s^{-1} litre^{-1})	R_{uncorr} ratio	η ratio	R_{corrl} (hPa s^{-1} litre^{-1})	$(\rho^*\eta)^{1/2}$ ratio	R_{corrm} (hPa s^{-1} litre^{-1})
ZEEP						
CON	18.4 (11.5–21.7)	0.99	1.11	16.6 (10.4–19.5)	1.10	16.7 (10.5–19.7)
N_2/O_2	17.1 (12.4–22.8)	1	1	17.1 (12.4–22.8)	1	17.1 (12.4–22.8)
N_2O/O_2	23.1 (14.5–27.7)	1.22	0.89	26.0 (16.3–31.2)	1.11	20.8 (13.1–25.0)
XEN/O_2	27.0 (21.3–37.7)	1.76	1.20	22.5 (18.2–31.4)	2.04	13.2 (10.7–18.5)
PEEP						
CON	15.7 (10.7–20.6)	0.97	1.11	14.2 (9.6–18.5)	1.10	14.3 (9.7–18.7)
N_2/O_2	17.4 (11.7–18.2)	1	1	17.4 (11.7–18.2)	1	17.4 (11.7–18.2)
N_2O/O_2	17.7 (14.4–24.9)	1.24	0.89	19.8 (16.2–28.0)	1.11	15.9 (13.0–22.5)
XEN/O_2	28.6 (22.5–34.7)	1.85	1.20	23.8 (18.8–28.9)	2.04	14.0 (11.0–17.0)

Statistics

All data are displayed as median and interquartile range. As there was no normal distribution, compliance and corrected airway resistance with each gas combination were compared with xenon values by Wilcoxon's test for paired values, with Bonferroni's correction for multiple testing. A P level of <0.05 was regarded significant.

Results

With tidal volume, inspiratory flow, and ventilatory frequency maintained constant, inspiratory pressure and, thus, calculated resistance is increased with xenon whereas comparable for the other gases. These uncorrected values together with compliance, tidal volume (calculated from flow data as stated above), and peak pressure are shown in the upper part of Table 3. With PEEP set to 10 hPa (10 cm H_2O), values are not changed except for P_{peak} (lower part of Table 3). There is, however, an increase in compliance close to significance after the introduction of PEEP with 100% oxygen ($P<0.07$).

Resistance with oxygen, nitrogen/oxygen, nitrous oxide/oxygen, and xenon/oxygen is opposed to normalized values for η and $(\rho^*\eta)^{1/2}$ and resistance corrected for those factors in Table 4. This table shows resistance after correction for normalized η (R_{corrl}, assuming laminar flow) and for normalized $(\rho^*\eta)^{1/2}$ (R_{corrm}, assuming mixed flow). Resistance corrected for laminar flow is very similar in all groups. When corrected for mixed flow, resistance tends to be lower with xenon compared with the other gases, but values are very close to each other and none of the differences are significant (however, xenon/oxygen compared with nitrous oxide/oxygen yielded $P<0.08$). There were no further differences in compliance (Table 3).

Systemic and pulmonary haemodynamics were within ±20% of control values, pulse oximetry saturation was between 97 and 100%, and end-tidal $P\text{CO}_2$ remained between 4.7 and 5.3 kPa throughout the study.

Discussion

Corrected resistance as shown in Table 4 is very similar for all the gas mixtures used in this study. When corrected for viscosity only, resistance is virtually the same in all groups, whilst following correction for $(\rho^*\eta)^{1/2}$, it tends to be lowest with xenon/oxygen. However, these differences are small and clinically irrelevant. When compliance is also unchanged, there is no evidence for a major effect of xenon anaesthesia on the respiratory system.

As haemodynamic and gas exchange parameters are completely stable, they should not have influenced the results.

There are some limitations to the results presented here: first, we determined the resistance of the whole respiratory system. Thus, resistance is slightly 'over-corrected' because the amount of tissue resistance and the influence of lung structure and the thorax (the so-called inertia), which are all independent of physical gas properties, were not subtracted. In order to do so, intrathoracic or oesophageal pressure would need to be measured. Nunn,[8] however, pointed out that measuring oesophageal pressure in the supine position poses some difficulties and stated that tissue resistance amounted to less than 20% of airway resistance whereas the contribution of the inertance to flow resistance is 'usually negligible'.[9] Consequently, we decided to look at the respiratory system as a whole.

Secondly, assuming a uniformly laminar or mixed flow pattern is a simplification of the complex fluid mechanics within the airways. However, using xenon as an inhaled anaesthetic introduces a new problem: the gases used so far are very similar in their physical properties. Thus, a certain range of inspiratory pressure, in an anaesthetized individual, has been established as normal, and increased values correlated with a change in airway calibre, lung structure, or both.

With xenon anaesthesia, inspiratory pressure is increased to a level that may alert the clinical anaesthetist. Such increased airway pressures have already been reported even with lower concentrations of xenon inhaled for diagnostic purposes.[10] Zhang and colleagues studied respiratory mechanics with xenon anaesthesia using 50% and 70% xenon in oxygen in open-chest dogs. They found an increase in calculated lung resistance with xenon by a factor of 1.4 as compared with nitrogen and nitrous oxide whereas there was no difference between the latter two.[3] Similar results have been reported by Calzia and co-workers who studied respiratory mechanics with xenon anaesthesia in pigs. They described an increase in airway resistance with 70% xenon by a factor of 1.4 compared with 70% nitrous oxide and of 1.5 compared with 70% nitrogen with oxygen.[2] These figures are close to our results before correction as we find an increase in calculated resistance by a factor of 1.4 for xenon compared with nitrous oxide and of 1.6 compared with nitrogen, each with 30% oxygen.

The influence of both density (ρ) and viscosity (η) on resistance depends on flow distribution: if flow is fully laminar, resistance at a given flow rate is determined by viscosity, and the influence of density increases with the development of turbulent flow. As the viscosity of xenon, in contrast to its density, is similar to that of the other gases, assuming laminar flow and correcting resistance for η would take into account only the smallest possible effect of xenon's physical properties. Even with this correction, resistances become very similar for all gas mixtures (Table 4). However, there are important sources of turbulence, for example the tracheal tube and the sudden increase in diameter at its tip within the tracheal lumen, which has been reported by Ingram and Pedley[11] to increase the calculated total resistance. Jaffrin and Kesic[6] have stated that there is a varying level of change from turbulent to laminar flow within the lung and that their proportions are difficult to determine. The approach suggested by Pedley and colleagues,[7] taking into account these sources of turbulence and, thus, assuming a mixed flow pattern rather than completely laminar flow, is a correction of the resistance for $(\rho{*}\eta)^{1/2}$. As the amount of turbulence in a certain airway at a given flow is again dependent on physical gas properties,[6] it is likely to be different for the gas mixtures used in this study which adds to the complexity of the problem. Thus, correction of the resistance for $(\rho{*}\eta)^{1/2}$ is used as an approximation, which yields small differences of no clinical relevance. The surprising finding is that resistance tends to be lower with xenon than with the other gases but this difference is probably caused by failure to subtract tissue resistance prior to correction, which leads to some 'over-correction' and by inaccuracy of the correction factor.

Although dose-dependent bronchodilating effects of isoflurane on pre-constricted airways have been found in various species,[12 13] it is still not clear if this also applies to unconstricted airways.[14 15] Isoflurane at least, does not add to beta-2-adrenergic bronchodilation after tracheal intubation.[16] We find no evidence of decreased airway resistance with isoflurane either 1.0% in nitrous oxide/oxygen or 1.5% in nitrogen/oxygen when compared with control in this study. A possible bronchodilation caused by ketamine premedication[17] may be neglected because the experiments began a least 2 h later. An increase in bronchomotor tone caused by thiopental[18] or remifentanil[19 20] cannot be excluded. However, it is unlikely to be relevant because all animals received the same doses and airway resistance was not dependent on the order in which experiments were performed but rather on individual differences. Thus, the use of anaesthetics with possible effects on airway resistance may have added to the variability but not substantially changed our results.

A lack of increase in airway pressure with xenon has only been described once. Lachmann and co-workers did not find differences in expiratory resistance in patients with xenon as compared with nitrous oxide anaesthesia although they did not report corrections for density or viscosity.[21] The reason for this finding is not clear whereas the increase in airway resistance reported in several experimental studies can be related to the lack of correction for physical properties of xenon. Calzia and colleagues[2] also described that after correction for physical properties, resistance did not increase but they did not conclude that the uncorrected resistance to gas flow might not be relevant for determining the effects of xenon anaesthesia on respiratory mechanics. For further studies using mechanical ventilation with xenon under clinical conditions, the simplified correction as suggested by Pedley and colleagues[7] may be useful because determining the exact quantities of laminar and turbulent flow is very difficult.

The introduction of PEEP produced an effect only during ventilation with 100% oxygen. Here, 10 hPa of PEEP increased (approaching significance) compliance which may be because the fact that partial collapse of alveoli is more likely to occur with a high inspired fraction of oxygen and that this collapse may be resolved with PEEP. However, PEEP did not change respiratory mechanics with any of the other gases. This is surprising in view of the reciprocal relationship between lung volume and airway resistance[9] but may be explained by the hypothesis that anaesthesia and paralysis did not induce relevant changes in lung volume. In contrast to adult humans and larger animals where functional residual capacity is reduced by supine positioning and anaesthesia, it was shown that this does not apply to smaller animals like dogs and small pigs.[22] Thus, even before the introduction of PEEP, our animals may have been on the flat part of the volume–resistance curve where there are only minor effects of lung volume on airway resistance. Although we did not determine lung volume we can exclude relevant changes from the fact that ventilator settings and tidal volumes were identical and expiratory flow always returned to zero in all animals.

In conclusion, inspiratory pressure is increased with inhalation of a mixture of xenon and 30% oxygen when compared with 100% oxygen, isoflurane/nitrogen/oxygen (1.5% in 70/30%), and isoflurane/nitrous oxide/oxygen (1.0% in 70/30%) with no change in compliance, in anaesthetized pigs. This increase is not different between

PEEP levels at 0 and 10 hPa. It is produced solely by the physical properties of xenon. Xenon does not increase airway resistance when values calculated from pressure and flow, are corrected for its physical properties. Such a correction should be performed in any further investigations of respiratory mechanics during xenon anaesthesia.

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Xenon increases total body oxygen consumption during isoflurane anaesthesia in dogs

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Background. This study was designed to examine whether the coupling between oxygen consumption ($\dot{V}O_2$) and cardiac output (CO) is maintained during xenon anaesthesia.

Methods. We studied the relationship between $\dot{V}O_2$ (indirect calorimetry) and CO (ultrasound flowmetry) by adding xenon to isoflurane anaesthesia in five chronically instrumented dogs. Different mixtures of xenon (70% and 50%) and isoflurane (0–1.4%) were compared with isoflurane alone (1.4% and 2.8%). In addition, the autonomic nervous system was blocked (using hexamethonium) to study its influence on $\dot{V}_{O_2}$ and CO during xenon anaesthesia.

Results. Mean (SEM) $\dot{V}O_2$ increased from 3.4 (0.1) ml kg^{-1} min^{-1} during 1.4% isoflurane to 3.7 (0.2) and 4.0 (0.1) ml kg^{-1} min^{-1} after addition of 70% and 50% xenon, respectively ($P<0.05$), whereas CO and arterial pressure remained essentially unchanged. In contrast, 2.8% isoflurane reduced both, $\dot{V}O_2$ [from 3.4 (0.1) to 3.1 (0.1) ml kg^{-1} min^{-1}] and CO [from 96 (5) to 70 (3) ml kg^{-1} min^{-1}] ($P<0.05$). $\dot{V}O_2$ and CO correlated closely during isoflurane anaesthesia alone and also in the presence of xenon (r^2=0.94 and 0.97, respectively), but the regression lines relating CO to $\dot{V}_{O_2}$ differed significantly between conditions, with the line in the presence of xenon showing a 0.3–0.6 ml kg^{-1} min^{-1} greater $\dot{V}O_2$ for any given CO. Following ganglionic blockade, 50% and 70% xenon elicited a similar increase in $\dot{V}O_2$, while CO and blood pressure were unchanged.

Conclusions. Metabolic regulation of blood flow is maintained during xenon anaesthesia, but cardiovascular stability is accompanied by increased $\dot{V}O_2$. The increase in $\dot{V}_{O_2}$ is independent of the autonomic nervous system and is probably caused by direct stimulation of the cellular metabolic rate.

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Metabolic regulation contributes to the adjustment of the circulation in order to meet tissue oxygen demand, and manifests itself as a linear relationship between blood flow (i.e. cardiac output [CO]), and oxygen consumption ($\dot{V}O_2$) during physiological conditions (e.g. physical exercise) in dogs[1] and humans.[2] We have recently shown that this fundamental principle is preserved during inhalation anaesthesia with the five volatile anaesthetics currently in use, unless the anaesthetic concentration exceeded 2 MAC.[3] This finding implies that increasing anaesthetic depth reduces $\dot{V}O_2$ and CO in parallel. We have also shown that the decrease in CO during inhalation anaesthesia is mainly a consequence of reduced metabolic rate rather than a direct side-effect of the anaesthetic.[3]

Recently, the noble gas xenon has been the subject of widespread interest because it has minimal effects on the cardiovascular system, leading to haemodynamic stability.[4] This cardiovascular stability has been explained by the fact that xenon does not alter myocardial function in humans[5] and animals[6] or in isolated hearts.[7] This haemodynamic stability with an unchanged CO despite an increase in anaesthetic depth is in contrast to findings with other volatile anaesthetics, which reduce $\dot{V}O_2$ and CO in parallel.[3]

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We therefore questioned whether, and to what extent, xenon alters $\dot{V}O_2$ and whether metabolic regulation of blood flow is maintained during xenon anaesthesia. To test this, we studied the relationship between CO and $\dot{V}O_2$ during different levels of xenon anaesthesia added to an isoflurane baseline in chronically instrumented dogs and compared the effects of xenon with those elicited by isoflurane.

Methods

The data derive from 15 experiments on five trained dogs (foxhounds of both sexes weighing 24–34 kg) studied with the approval of the District Governmental Animal Investigation Committee. Each dog was assigned to each of the three intervention groups with an interval of at least 1 week between successive experiments in the same animal, so that each dog served as its own control.

Surgery

Several weeks before the experiments, the dogs were operated on under general anaesthesia (enflurane/nitrous oxide + fentanyl) and aseptic conditions. For blood pressure recording and blood sampling, both carotid arteries were exteriorized in skin loops.[8] Ultrasound transit-time flow transducers were implanted around the pulmonary artery through a left-sided thoracotomy for continuous recording of CO.

Measurements

Cardiac output

Blood flow through the pulmonary artery was measured continuously with an ultrasound transit-time system (T101, Transonic Systems, Ithaca, NY, USA). Each flow transducer (20–24 mm S-series with silicone shielded U-reflector; Transonic Systems) was calibrated *in vitro* before implantation and *in vivo* at least 3 weeks after implantation, using the Fick principle from $\dot{V}O_2$ and the arterial-to-mixed venous oxygen content difference ($C(a-\bar{v})_{O_2}$) measured with a galvanic cell (Lex-O$_2$-Con-TL®, Lexington Instruments, Waltham, USA), resulting in high precision, as described previously.[9]

Oxygen uptake ($\dot{V}O_2$)

$\dot{V}O_2$ (at standard temperature [273 K], pressure [760 mmHg] and dry P_{H_2O} 0 mm Hg]) was measured continuously by indirect calorimetry with a Deltatrac II® Metabolic Monitor (Datex-Engstrom Division, Instrumentarium Corp., Helsinki, Finland). Before each experiment, the gas sensors were calibrated with air and a gas mixture containing 95.0 (0.05)% O_2 and 5.0 (0.03)% CO_2, and the measurement of $\dot{V}O_2$ was calibrated by burning 5 ml pure ethanol (alcohol burning test kit, Datex-Engstrom, Helsinki, Finland).

Burning of alcohol was also repeated in the presence of 50 and 70% xenon to ensure that the high density of xenon did not alter the flow constant of the built-in flow generator. In addition, baseline stability of the gas sensors was tested by feeding xenon to the mixing chamber of the Deltatrac II to check if xenon alters O_2 and CO_2 measurements.

During spontaneous breathing in awake dogs, $\dot{V}O_2$ was measured with a flow-through technique (canopy mode), as described previously,[10] which calculated $\dot{V}O_2$ from the difference of inspired and expired oxygen concentration and the constant gas flow through the built-in flow generator. For this purpose, a transparent plastic canopy was fixed above the dog's head and upper trunk, allowing room air to enter at the edges as air was sucked continuously through the Deltatrac II for analysis. A canopy volume of approximately 70 litres and a flow generator rate of about 40 litre min^{-1} resulted in a system time constant of 1.75 min.

During anaesthesia and controlled ventilation $\dot{V}O_2$ was measured directly from the respiratory gases. The expired air was collected and fed to the mixing chamber of the Deltatrac II (respiration mode, a collection technique with a time constant of 1 min). As a cross-check of the Deltatrac II measurements, we also intermittently measured $\dot{V}O_2$ from the product of CO and $C(a-\bar{v})_{O_2}$ (pulmonary artery catheter). In agreement with others,[11 12] the precision of this device was 3.5% (average coefficient of variation) and the accuracy was 0.1 ml min^{-1}, with 95% confidence intervals of −4.8 to 5.0 ml min^{-1}.

Arterial pressure

Arterial pressure was measured electromanometrically (Statham P-23ID, Elk Grove, USA) through a catheter in the carotid artery. The electromanometer was calibrated with a mercury manometer and referenced to the processus spinosus of the 7th vertebra while the dogs were lying on its right side. Mean arterial pressure (MAP) was measured by integration from the original pressure signal.

Heart rate and RR intervals

HR and RR were determined from a standard ECG (surface electrodes) used for triggering a rate meter, which provided a continuous recording of the heart periods (RR intervals).

All variables were recorded continuously on an eight-channel polygraph (model RS 3800, Gould Inc., Cleveland, OH, USA) and simultaneously stored on the hard disk of a conventional personal computer for further analysis after analog-to-digital conversion with a rate of 400 Hz. During anaesthesia, respiratory gases and vapour concentrations were measured continuously at the endotracheal tube orifice by infrared spectroscopy (Capnomac® Ultima SV, Datex-Engstrom, Helsinki, Finland). We also intermittently determined arterial blood gas tensions, oxygen saturation, and pH (ABL3®, Radiometer, Copenhagen, Denmark).

Derived variables

Heart rate variability

HR variability (HRV), an indicator of the activity of the autonomic nervous system, was studied as recommended.[13] For this purpose, the original ECG signal, free of aberrant

ECG complexes and artefacts, was analysed during the last 5 min of each intervention (CHART®, ADInstruments, Castle Hill, Australia). HRV was analysed in the frequency domain and calculated as activity in the high frequency (HF: 0.15–0.5 Hz) and low frequency (LF: 0.04–0.15 Hz) range, the former showing predominantly vagal activity and the latter mainly sympathetic activity.[13] Autonomic balance was assessed by calculating the quotient of power in the high frequency (nuHF) and low frequency (nuLF) range, respectively, divided by total power (sum of HF and LF power).[13]

Experimental protocol

All experiments were carried out with awake dogs in the basal metabolic state (food withheld for 12 h with free access to water) and under standardized experimental conditions (lightly dimmed laboratory at thermoneutral temperature for dogs of 24°C).[14] To ensure complete elimination of the inhalation anaesthetic, successive experiments were performed at least 1 week apart.

After instrumentation and connecting the animal to the recording system, we waited for 30 min until all variables had reached steady state. The experiments started with baseline measurements for a further 30 min while the animal breathed spontaneously. Following the insertion of the endotracheal tube (intravenous injection of propofol 3 mg kg^{-1}), the animal's lungs were ventilated with 25% oxygen in nitrogen (tidal volume about 10 ml kg^{-1} and a rate of 14 bpm to maintain normocarbia). Isoflurane was added and adjusted to an end-tidal concentration of 1.4% (1 MAC).[15] We then waited 30 min, in order to minimize interaction with propofol. During this equilibration period, a pulmonary artery catheter was advanced from the animal's hind limb to obtain mixed venous blood samples. Thereafter, the following experiments were performed.

Oxygen uptake during xenon anaesthesia (n=5)

To evaluate whether xenon alters oxygen uptake, the following three mixtures were administered to each dog, but in a sequence which was randomized for each dog: FE′iso = 1.4% + FIxe = 50%, FE′iso = 1.4% + FIxe = 70%, FE′iso = 2.8%. The randomization resulted in two of the six possible sequences being used in two dogs each and one in another dog. Each gas mixture was maintained for 20 min to reach steady state. Before the end of the experiment, the animal was ventilated again with isoflurane 1.4% (1 MAC) in air to check whether $\dot{V}O_2$ and CO returned to control values.

Metabolic regulation of CO during xenon anaesthesia (n=5)

In a second series of experiments on the same animals, the interventions of group 1 were repeated (with randomization leading to one of the six possible sequences being used in three dogs and one in two dogs) and extended by two additional mixtures: FE′iso = 0.7% + FIxe = 50%, and FIxe = 70%, always in that sequence. The total of five different mixtures was again administered between two periods of FE′iso = 1.4%. Thus, we studied the dogs under a total of four interventions in the presence of xenon and under two different interventions with isoflurane, alone plus the awake state.

Oxygen uptake during ganglionic blockade (n=5)

After completion of groups 1 and 2, we studied the same animals again in order to see whether the increase in $\dot{V}O_2$ is of central or peripheral origin. For this purpose, hexamethonium, a ganglionic blocking agent, 7.5 mg kg^{-1} was injected before induction of anaesthesia, followed by continuous infusion of 7.5 mg kg^{-1} h^{-1}. Thereafter, the following two mixtures were administered to each dog: FE′iso = 1.4% + FIxe = 50%, FE′iso = 1.4% + FIxe = 70%, with randomization leading to one sequence being used in four dogs and the other in one dog.

Data analysis and statistics

Results are given as mean (SEM) and were compared using a paired *t* test. The resulting *P* values were corrected for multiple testing according to the Bonferroni procedure. In the case of repeated experiments in one animal, the results from individual dogs were averaged. CO was regressed on $\dot{V}O_2$ during the awake state and isoflurane anaesthesia, as well as during anaesthesia in the presence of xenon, and results were compared using an *F* test for differences between regression lines. The slopes of the individual relationships between $\dot{V}O_2$ and CO are given as mean slope and confidence interval. The effects on HR, MAP, systemic vascular resistance and $C(a-\bar{v})_{O_2}$ were compared by an analysis of variance for repeated measures (ANOVA), followed by Fisher's protected least significant difference test[16] if appropriate. Statistical significance was assumed when $P<0.05$.

Results

In general, $\dot{V}O_2$ increased significantly while CO remained essentially constant when xenon was added to isoflurane baseline anaesthesia. In detail, with the addition of xenon (50% and 70%) during isoflurane anaesthesia, $\dot{V}O_2$ increased from 3.4 (0.1) to 4.0 (0.1) and to 3.7 (0.2) ml kg^{-1} min^{-1} ($P<0.05$), respectively, whereas CO remained essentially unchanged (Fig. 1). In contrast, with the transition from awake to 1 MAC and eventually 2 MAC isoflurane alone, $\dot{V}O_2$ decreased by about 25% from 4.1 (0.2) ml kg^{-1} min^{-1} (awake) to 3.1 (0.1) ml kg^{-1} min^{-1} (2 MAC isoflurane). In parallel, CO decreased by about 40% from 121 (6) ml kg^{-1} min^{-1} (awake) to 70 (3) ml kg^{-1} min^{-1} (2 MAC isoflurane).

To answer the question of whether metabolic regulation of blood flow is maintained during xenon anaesthesia, we analysed the relationship between CO and $\dot{V}O_2$ in the presence and absence of xenon (Fig. 2). In both conditions, CO increased linearly with $\dot{V}O_2$ (r^2=0.97 and 0.94, respect-

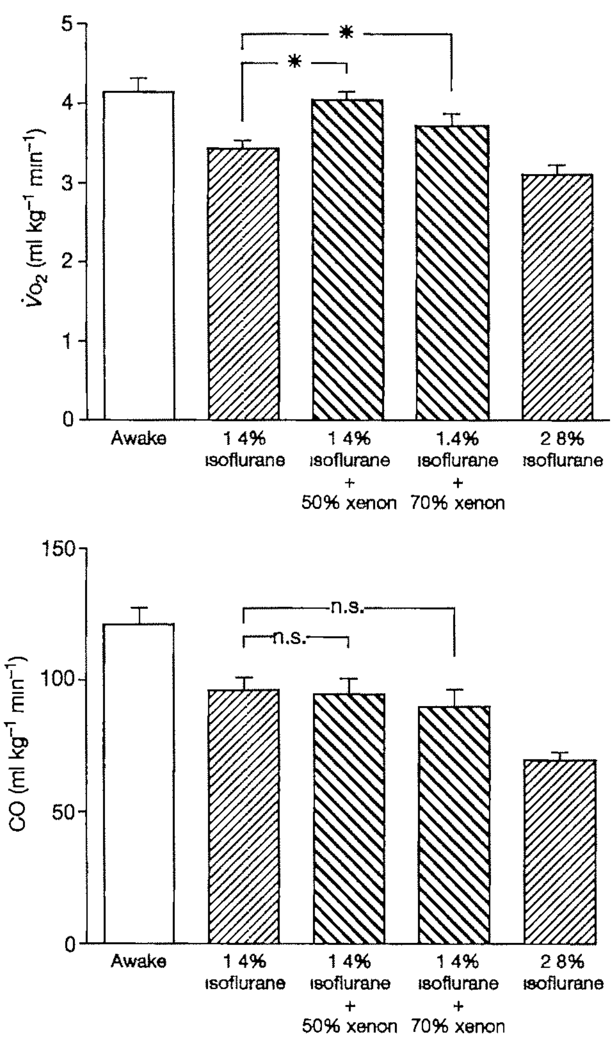

Fig 1 Oxygen consumption (Vo_2) and cardiac output (CO) in the awake state, during isoflurane anaesthesia 1.4% and 2.8% and after adding 50% and 70% xenon to an isoflurane baseline. Data are mean±SEM from five dogs. Note the significant increase in Vo_2 (*$P<0.05$) in the presence of xenon compared with 1.4% isoflurane, whereas CO remained essentially unchanged. n.s., not significant

ively) and the regression lines differed significantly ($P<0.05$). For any given CO, $\dot{V}o_2$ was 0.3–0.6 ml kg^{-1} min^{-1} greater in the presence of xenon. Conversely, CO is 14–21 ml kg^{-1} min^{-1} lower for a given $\dot{V}o_2$ when xenon is present.

To distinguish whether the increase in $\dot{V}o_2$ results from a central or peripheral effect, we analysed HRV to assess sympathovagal balance (see Fig. 3) and, in additional experiments, added xenon to the respiratory gases after ganglionic blockade (pretreatment with hexamethonium). After increasing anaesthetic depth with xenon or isoflurane, nuHF tended to increase and nuLF tended to decrease, indicating a shift towards vagal activation.

After ganglionic blockade (Fig. 4), $\dot{V}o_2$ increased during the addition of 50% or 70% xenon to 1.4% isoflurane anaesthesia from 3.4 (0.2) ml kg^{-1} min^{-1} to 4.0 (0.2) and 3.7 (0.3), respectively, whereas CO remained almost unchanged. Thus, in the presence or absence of ganglionic blockade, xenon elicited similar effects on Vo_2 and CO, albeit at a lower CO (compare with Fig. 1).

$C(a-\bar{v})_{O_2}$ tended to increase from 3.7 (0.2) ml 100 ml^{-1} during 1 MAC isoflurane anaesthesia to 4.1 (0.5) ml 100 ml^{-1} and finally 4.4 (0.5) ml 100 ml^{-1} with the addition of 50% and 70% xenon, respectively (Table 1). Nevertheless, $C(a-\bar{v})_{O_2}$ increased with increasing anaesthetic depth in a parallel manner in the presence and absence of xenon – except for 70% xenon alone (Fig. 5). However, the error bars show that, at any given MAC, the differences between isoflurane and xenon (with or without isoflurane) are not significant. It is worthy of note that HR (105 [5] beats min^{-1} during 1.4% isoflurane), decreased on the addition of xenon 50% and 70% to 95 (2) and 92 (2) beats min^{-1}, respectively, which was in parallel with vagal activation, as indicated from the analysis of HRV (Fig. 3). Arterial pressure, however, did not change on the addition of xenon to 1.4% isoflurane anaesthesia.

Discussion

Our experiments show that, within the range of conditions studied, adding xenon to isoflurane baseline anaesthesia increases Vo_2. This increase in Vo_2 is independent of the autonomic nervous system and is probably caused by an increase in the cellular metabolic rate. Furthermore, metabolic regulation of blood flow is maintained during xenon anaesthesia, as shown by the linear relationship between CO and Vo_2. Accordingly, haemodynamic stability when adding xenon to isoflurane baseline anaesthesia is accompanied by an increase in the whole body metabolic rate ($\dot{V}o_2$).

Critique of methods

Attempts to compare the effects of different anaesthetics on CO and Vo_2 rest primarily on the precision of the measurement methods. This question is of particular interest because Vo_2 during xenon anaesthesia has not been measured before.

$\dot{V}o_2$ was measured with the Deltatrac II at a precision of 3.5%. The precision is independent of the collection mode, flow through, or canopy,[12 17 18] and is not influenced by the addition of volatile anaesthetics if a correction for the exhaled concentration of the anaesthetic is made.[19] Moreover, the four times greater density of xenon[4] compared with air did not alter the flow constant of the flow generator, and xenon did not influence oxygen – or carbon dioxide – measurements in our experiments. Accordingly, measurements of Vo_2 using a Deltatrac II were sufficiently precise to evaluate $\dot{V}o_2$ during anaesthesia with xenon in relationship to isoflurane.

CO was measured by ultrasound transit-time flow probes placed around the pulmonary artery. These probes had been

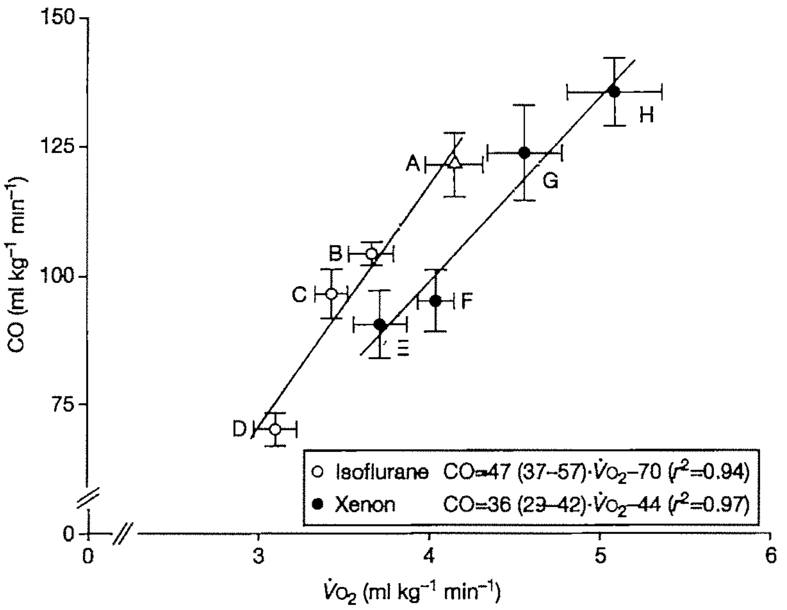

Fig 2 Relationship between cardiac output (CO) and oxygen consumption ($\dot{V}O_2$) in the awake state (A) and during isoflurane anaesthesia (1.4% [B, C] and 2.8% [D]) in comparison with xenon anaesthesia (70% and 50% xenon with 1.4% isoflurane [E, F], 50% xenon with 0.7% isoflurane [G] and 70% xenon alone [H]). Values are given as mean±SEM from five dogs. Note the close relationship between $\dot{V}O_2$ and CO during the awake state and during isoflurane anaesthesia (open circles), as well as in the presence of xenon (closed circles), with different regression lines ($P<0.05$)

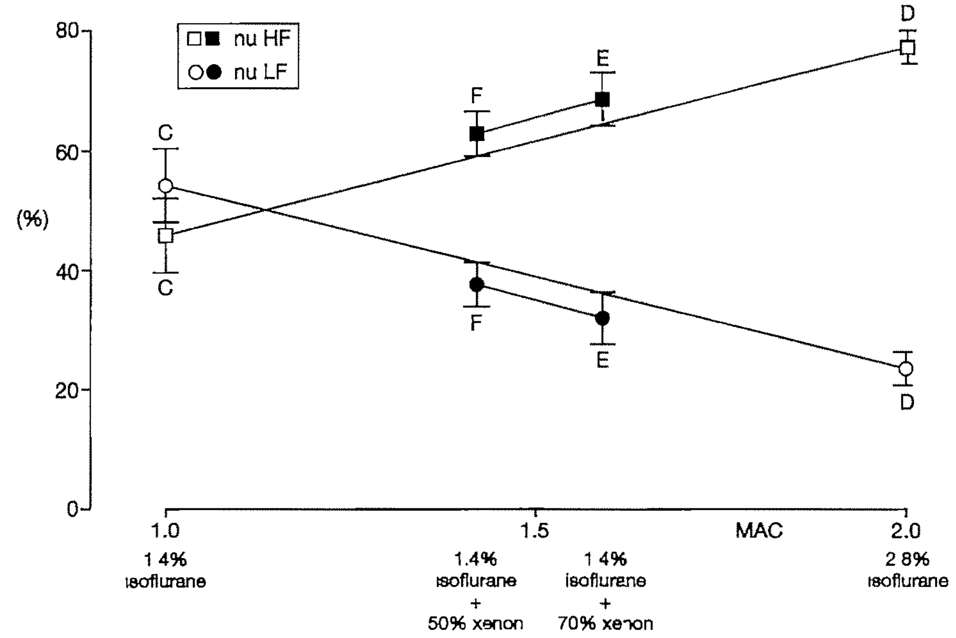

Fig 3 Sympathovagal balance analysed as heart rate variability in the frequency domain and expressed as high and low frequency normalized units (nuHF [squares] and nuLF [circles], respectively) during isoflurane anaesthesia ([open symbols] 1.4% [C], 2.8% [D]) and after adding xenon (70% and 50% [closed symbols] to 1.4% isoflurane [E, F]). Values are mean±SEM from five dogs. Note the parallel shift towards vagal activation (nuHF) when the anaesthetic depth is increased by adding xenon or by increasing the isoflurane alone

calibrated *in vitro* by a given saline flow and, after implantation, by the Fick principle from $\dot{V}O_2$ and $C(a-\bar{v})_{O_2}$. Implantation around the pulmonary artery was chosen to obtain the entire cardiac output, which cannot be measured with flow probes placed around the aorta because coronary flow is not detected. These probes have been shown to continuously measure CO precisely over several years.[9]

The accuracy of our three independent measurement methods ($\dot{V}O_2$, CO and $C(a-\bar{v})_{O_2}$) can be cross-checked

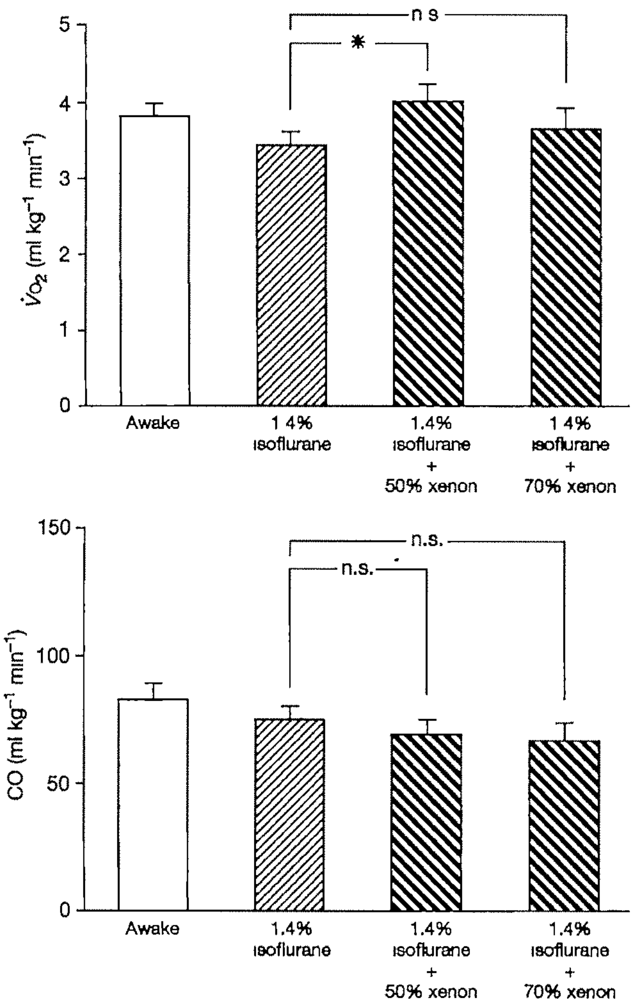

Fig 4 Oxygen consumption (VO_2) and cardiac output (CO) after ganglionic blockade with hexamethonium in the awake state, during 1.4% isoflurane anaesthesia alone and after adding 50% and 70% xenon to isoflurane baseline anaesthesia Data are mean±SEM from five dogs. Note that VO_2 increased ($P<0.05$), whereas CO remained almost unchanged (n s., not significant), as in the absence of ganglionic blockade (compare with Fig. 1).

using the Fick equation. Adding 50% xenon to 1.4% isoflurane did not change CO, so that changes in $\dot{V}O_2$ and $C(a-\bar{v})_{O_2}$ should balance each other. In fact, VO_2 and $C(a-\bar{v})_{O_2}$ increased by 18% and 9%, respectively, confirming that CO was an essentially unchanged (calculation would yield 108%), with only 8% difference between independent measurement (ultrasound flowmetry) and calculation. This accuracy is likewise confirmed by the mean difference between measured and calculated $C(a-\bar{v})_{O_2}$ values, which was only 3.9 (3.1)%.

Propofol, needed for inserting the endotracheal tube, may have influenced the effects of the inhalation anaesthetics. However, the plasma concentration of propofol should have decayed to a fraction of the initial peak within 10 min because of redistribution (half-life of the α-phase of about 2 min) and, thereafter, more gradually as elimination continues (half-life of the γ-phase of about 4 h)[20] Moreover, in pilot experiments, all dogs resumed their normal activity and behaviour within 15 min after the injection of a single dose of propofol. Accordingly, the additive anaesthetic effects of propofol should have been small, and comparable for all interventions.

The dosage of hexamethonium used in our study was appropriate to eliminate the influence of the autonomic nervous system, as indicated not only from the literature[21] but also from our own experiments, in which arterial pressure and HR did not change after 45 s of bilateral carotid artery occlusion. In contrast, before hexamethonium administration, arterial pressure increased by about 40 mm Hg and HR by 20 beats min^{-1}. Thus, our methods should have been appropriate for deriving reliable measurements.

Interpretation of results

Metabolic regulation of blood flow manifests itself as a linear relationship between CO and VO_2, during both physiological conditions[1] and inhalation anaesthesia.[3] In

Table 1 Haemodynamic variables and blood gas tensions in the awake state and during combinations of xenon and isoflurane anaesthesia in the intact dog and after ganglionic blockade with hexamethonium Data are mean (SEM) from 15 experiments in five dogs $^*P<0.05$ *vs* awake, $^\dagger P<0.05$ *vs* 1.4% isoflurane (1st) HR, heart rate, MAP, mean arterial pressure; SVR, systemic vascular resistance; Pa_{O_2} and Pa_{CO_2}, arterial oxygen and carbon dioxide gas tensions, respectively; Sa_{O_2}, arterial oxygen saturation, $C(a-\bar{v})_{O_2}$, mixed venous oxygen content difference

	Isoflurane (vol %)	Xenon (vol %)	HR (beats min^{-1})	MAP (mm Hg)	SVR (mm Hg litre^{-1} min)	Pa_{O_2} (mm Hg)	Pa_{CO_2} (mm Hg)	pH	Sa_{O_2} (%)	$C(a-\bar{v})_{O_2}$ (ml 100 ml^{-1})
Intact autonomic nervous system	Awake		82 (3)	98 (3)	25 (1)	94 (2)	37 (1)	7.35 (0.01)	95 (1)	
	1.4 (1st)		105 (5)*	63 (3)*	20 (1)*	123 (4)*	37 (1)	7.33 (0.01)	97 (1)	3.7 (0.2)
	1.4 (2nd)		110 (4)*	71 (2)*†	21 (1)*	126 (4)*	41 (1)	7.31 (0.01)	97 (1)	3.7 (0.2)
	2.8		102 (1)*	42 (2)*†	19 (1)*	119 (7)*	41 (1)	7.30 (0.01)	97 (1)	5.1 (0.5)†
		70	110 (4)*	115 (3*†	26 (1)†	120 (2)*	44 (1)	7.29 (0.02)	97 (1)	4.1 (0.4)
	0.7	50	107 (7)*	85 (3)*†	21 (2)*	116 (3)*	43 (1)	7.29 (0.02)	96 (1)	3.3 (0.2)
	1.4	50	95 (2)*	63 (4)*	21 (1)*	121 (6)*	41 (1)	7.31 (0.01)	97 (1)	4.1 (0.5)
	1.4	70	92 (2)†	65 (5)*	23 (1)*†	121 (5)*	42 (1)	7.29 (0.01)	97 (1)	4.4 (0.5)
Plus hexamethonium	Awake		137 (4)	88 (3)	36 (3)	83 (4)	40 (2)	7.34 (0.01)	93 (1)	
	1.4		117 (4)*	61 (3)*	27 (1)*	124 (7)*	38 (1)	7.34 (0.01)	97 (1)	3.8 (0.4)
	1.4	50	112 (4)*	55 (3)*	27 (3)*	117 (5)*	42 (1)	7.30 (0.01)	97 (1)	4.0 (0.4)
	1.4	70	111 (3)*†	52 (3)*†	26 (3)*	115 (5)*	43 (2)	7.29 (0.01)	96 (1)	4.0 (0.4)

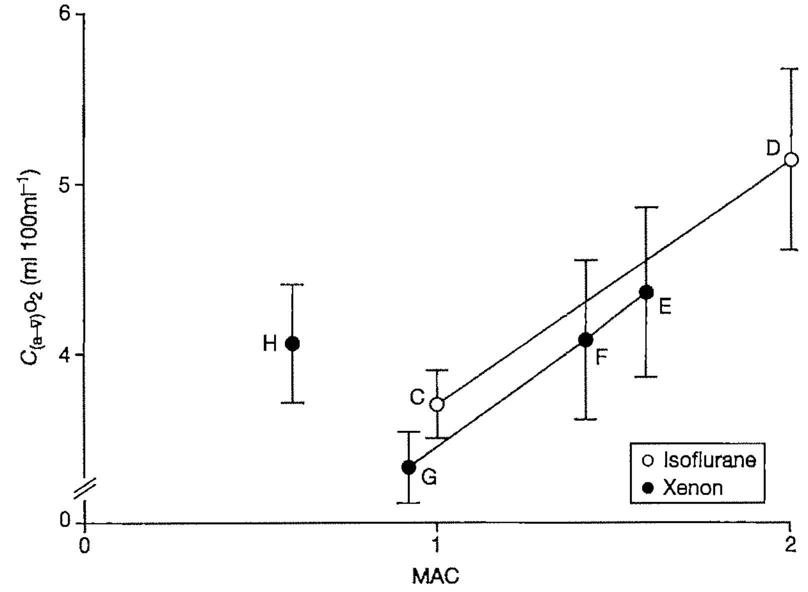

Fig 5 Arterial to mixed venous oxygen content difference ($C(a-\bar{v})_{O_2}$) during isoflurane anaesthesia (1.4% [C] and 2.8% [D]) in comparison with xenon anaesthesia (70% and 50% xenon with 1.4% isoflurane [E, F], 50% xenon with 0.7% isoflurane [G] and 70% xenon alone [H]) plotted against combined MAC Data are mean±SEM from five dogs. Note that in the range above 1 MAC, $C(a-\bar{v})_{O_2}$ tended to increase with increasing anaesthetic depth in a parallel manner in the presence and absence of xenon

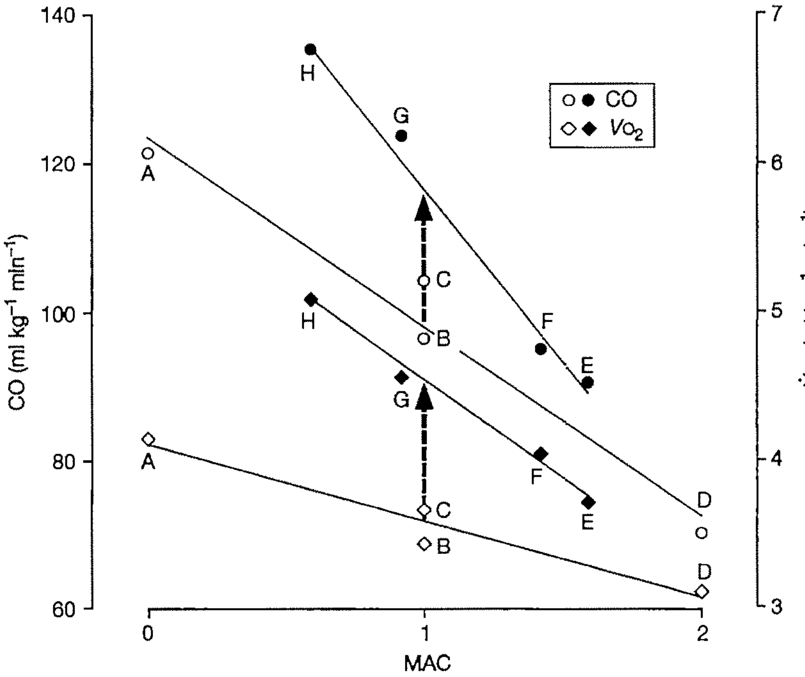

Fig 6 Oxygen consumption ($\dot{V}O_2$ [diamonds]) and cardiac output (CO [circles]) in relation to the anaesthetic depth (MAC), in the awake state (A) and during isoflurane anaesthesia (1 4% [B, C] and 2.8% [D]) in comparison with xenon anaesthesia (70% and 50% xenon with 1.4% isoflurane [E, F], 50% xenon with 0.7% isoflurane [G] and 70% xenon alone [H]). Values are means from five dogs. Both variables correlate closely in the absence (open symbols) and presence (closed symbols) of xenon. Note that substituting xenon for parts of the isoflurane (see arrows) would lead to an increase in CO and $\dot{V}O_2$, with the effects of xenon tending to decrease as MAC increases

this context, $\dot{V}O_2$ is considered the independent variable and thus determines CO, and not vice versa.[3] In our experiments during inhalation anaesthesia with isoflurane, CO and $\dot{V}O_2$ decreased from the awake state (basal metabolic conditions) to 2 MAC (points A–D in Fig. 2). This relationship was linear, with a slope of CO *vs* $\dot{V}O_2$ of 47, confirming our previous observations.[3] In that study,[3] we could also show that the relationship between CO and $\dot{V}O_2$ did not differ significantly between the five most commonly used volatile anaesthetics.[3]

In contrast to the effects of these volatile anaesthetics, increasing anaesthetic depth from 1 MAC isoflurane with xenon by about 0.5 MAC (MAC value of 119% in dogs[22]) increased VO_2 while CO remained essentially unchanged. Cardiovascular stability during xenon anaesthesia has generally been observed in healthy individuals,[23 24] as well as in dogs with dilated cardiomyopathy.[6] Moreover, xenon had only minimal effects on myocardial contractility *in vivo*[5 25] and maintained cardiovascular stability during surgical stimulation.[26] However, total body oxygen consumption, the main determinant of CO, has not been measured during xenon anaesthesia before.

Increases in $\dot{V}O_2$ could be related to either an increase in efferent sympathetic activity or a direct stimulating effect on the cellular metabolic rate. To test the contribution of the autonomic nervous system, we repeated the experiments after autonomic blockade. The increase in $\dot{V}O_2$ during xenon anaesthesia was identical after ganglionic blockade, thus excluding increased sympathetic activity and suggesting a direct effect on cellular metabolic rate. However, there are no studies of the interaction between xenon and the molecular mechanisms of metabolism, and explanations of this phenomenon are beyond the scope of our experiments. The absence of sympathetic contribution to the increase in $\dot{V}O_2$ is confirmed by the shift towards vagal activation, as indicated from the analysis of HRV in the experiments with the intact autonomic nervous system. Similar effects of xenon on the autonomic nervous system were previously observed in humans.[27] In conclusion, xenon increases $\dot{V}O_2$ most likely by directly stimulating the cellular metabolic rate.

Only myocardial oxygen consumption has been previously studied in detail during xenon anaesthesia, but this did not change either *in vivo*[25] or in isolated hearts.[7] However, myocardial oxygen consumption contributes only 10–15% to total body $\dot{V}O_2$, and changes in myocardial oxygen consumption may not necessarily parallel changes in total body VO_2

When anaesthetic depth changed, $\dot{V}O_2$ and CO were linearly related in the presence of xenon, much like in the presence of volatile anaesthetics. However, the regression lines for xenon with and without isoflurane, and for isoflurane alone, differed significantly (Fig. 2). At any given CO, VO_2 was greater in the presence of xenon. If, in addition, CO and $\dot{V}O_2$ are plotted against MAC, at least one more interpretation can be obtained (Fig. 6). Over the range of anaesthetic depths studied (below 2 MAC), substituting xenon for a proportion of the isoflurane (see arrows) would lead to an increase in CO and $\dot{V}O_2$, with the effects of xenon tending to decrease as MAC increases. However, this interpretation has to be drawn with caution since it depends on the MAC of xenon, which has only been measured once in dogs[22] and, in contrast to the other inhalation anaesthetics, differed by a factor of two between dogs and humans. It is also worth noting that HR decreased slightly during xenon anaesthesia in parallel with vagal activation, a phenomenon which has likewise been shown for the volatile anaesthetics.[28] Thus, changes in HR during xenon anaesthesia are most likely caused by vagal activation. This interpretation is in accordance with the absence of this effect in isolated hearts.[7] Accordingly, regulation of HR during xenon anaesthesia apparently does not differ from that during isoflurane anaesthesia.

In summary, adding xenon to isoflurane baseline anaesthesia increases $\dot{V}O_2$, while haemodynamics, including CO, are essentially unchanged. Metabolic regulation of blood flow is maintained at a higher tissue oxygen extraction rate. When xenon is substituted for a proportion of the isoflurane, both $\dot{V}O_2$ and CO are increased.

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Does ester hydrolysis change the *in vitro* degradation rate of cisatracurium and atracurium?

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Background. We assessed the role of ester hydrolysis as an additional degradation mechanism to Hofmann elimination in the breakdown of cisatracurium and atracurium.

Methods. Cisatracurium and atracurium were incubated in phosphate buffer (pH 7.4, 37°C) with and without the addition of carboxylesterase. Control measurements with an added esterase inhibitor were performed separately. Cisatracurium/atracurium and their degradation products, laudanosine and monoquaternary acid, were analysed using high-pressure liquid chromatography.

Results. Degradation of cisatracurium and atracurium proceeded exponentially, and after addition of carboxylesterase, no significant differences in the degradation rates were found. Neither an increase in carboxylesterase activity nor the addition of esterase inhibitor showed any effect. However, areas under the peaks of the chromatogram representing monoquaternary acid increased during incubation with esterase.

Conclusion. The rate-limiting step in the degradation of cisatracurium/atracurium is Hofmann elimination. Ester hydrolysis is involved in the second degradation step that forms monoquaternary acid, but its contribution to the total elimination rate is negligible.

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Atracurium besylate and its 1R-*cis*, 1R′-*cis* isomer, cisatracurium, are non-depolarizing neuromuscular blocking drugs of intermediate duration of action. Both drugs undergo Hofmann elimination, a process dependent on pH and temperature. This unique pharmacological property provides an organ-independent degradation pathway. Atracurium and, in particular, cisatracurium with its 3- to 5-fold higher neuromuscular blocking potency but lower histamine releasing potential, are widely used clinically.[1]

The degradation of cisatracurium and atracurium via Hofmann elimination has been thoroughly investigated. Two comprehensive reviews with special emphasis on the pharmacokinetics and the main degradation pathways of cisatracurium and atracurium were published in 1999.[1 2] *In vitro* and *in vivo* studies suggested that Hofmann elimination produces 30–70% of the total drug elimination in man and mammals.[1]

It has been shown[3] that the rate of Hofmann elimination depends on the composition and ion activity/concentration of the incubation medium, which at least in part, may explain the rather large differences in elimination rates between plasma and various buffer solutions, even at identical pH and temperature.[4 5]

The role of ester hydrolysis as a second degradation pathway is controversial. In humans, some authors consider ester hydrolysis to be a major degradation pathway.[4 6] Other authors assume the contribution of ester hydrolysis to the metabolism of atracurium to be small but nevertheless relevant, but they cannot find any significant role for this pathway in the metabolism of cisatracurium.[7–10]

The exact nature and type of esterases involved in ester hydrolysis of cisatracurium and atracurium is unknown, but most likely, the non-specific aliesterase (carboxylesterase) facilitates the hydrolysis.[4] No data are yet available on the

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potential effect of carboxylesterase on the degradation rates of these two neuromuscular blocking drugs. The aim of the present study was, therefore, to determine whether and how the *in vitro* degradation rates of cisatracurium and atracurium are influenced by ester hydrolysis.

Material and methods

Compounds and reagents

Cisatracurium besylate and atracurium besylate were supplied by Glaxo-Wellcome Pharma, Vienna, Austria. Acetonitrile (Promochem, Wesel, Germany) was high-pressure liquid chromatography (HPLC) grade. Carboxylesterase (CE) from porcine liver (EC 3.1.1.1) and bis-(*p*-nitrophenyl) phosphate (BPNP) were obtained from Sigma, St Louis, MO, USA. All other reagents were obtained from E. Merck (Darmstadt, Germany) and were of analytical grade. Buffers for calibration of the pH-meter were obtained from Radiometer (Copenhagen, Denmark).

Incubations

The commercially available solution of cisatracurium (2.15 mmol litre^{-1}) was diluted (1:2) with 5 mmol litre^{-1} H_2SO_4. A volume of 20 µl of the diluted solution was then added to 10 ml of the incubation buffer, mixed well, and incubated at 37°C. Similarly, the commercially available solution of atracurium (8 mmol litre^{-1}) was diluted (1:10) with H_2SO_4 5 mmol litre^{-1}, and 25 µl of the diluted solution were added to 10 ml of the incubation buffer.

The buffer was a 50 mmol litre^{-1} phosphate buffer (Na_2HPO_4+NaH_2PO_4) with NaCl 136.8 mmol litre^{-1} and KCl 2.7 mmol litre^{-1}.[8] The pH was adjusted to 7.4 at 37°C with either the acidic or the basic component of the buffer as necessary. At the end of the incubation period, the pH was rechecked and the incubation experiment rejected if the measured pH value differed from 7.40 by more than ±0.05.

Incubations of cisatracurium were performed in phosphate buffer (experimental series C1, cisatr), and in phosphate buffer after addition of 20 (C2, cisatr+20CE) and 100 (C3, cisatr+100CE) unit litre^{-1} carboxylesterase (esterase EC 3.1.1.1). In order to check whether protein *per se* influences the degradation of cisatracurium, separate measurements with the same concentration of enzyme were performed in the presence of the esterase inhibitor, BPNP. The series with the combined addition of carboxylesterase and esterase inhibitor BPNP (CE 20 unit litre^{-1} and BPNP 10 µmol litre^{-1}, and CE 100 unit litre^{-1} and BPNP 50 µmol litre^{-1}, respectively) are denoted as C4 (cisatr+20CE+10BPNP) and C5 (cisatr+100CE+50BPNP). Incubations with buffers containing only cisatracurium and esterase inhibitor BPNP (10 µmol litre^{-1}) are denoted C6 (cisatr+10BPNP).

Corresponding incubations of atracurium in phosphate buffer are denoted as A1 (atr) and the incubation series in phosphate buffer after addition of CE 20 and 100 unit litre^{-1} are denoted as A2 (atr+20CE) and A3 (atr+100CE), respectively. The series with the combined addition of carboxylesterase and esterase inhibitor BPNP (CE 20 unit litre^{-1} and BPNP 10 µmol litre^{-1}, and CE 100 unit litre^{-1} and BPNP 50 µmol litre^{-1}, respectively) are denoted as A4 (atr+20CE+10BPNP) and A5 (atr+100CE+50BPNP). Incubations with buffers containing only atracurium and esterase inhibitor BPNP (BPNP 10 µmol litre^{-1}) are denoted A6 (atr+10BPNP).

Before the addition of cisatracurium or atracurium, the incubation solutions were pre-incubated with the supplements for 30 min at 37°C. After defined time intervals (0, 10, 20, 30, 60, 90, 120, 180, and 240 min), 0.5 ml aliquots were withdrawn, acidified with 10 µl of H_2SO_4 1 mol litre^{-1} and frozen (–20°C) until measurement. The concentrations of cisatracurium, atracurium, and laudanosine were measured by HPLC using an assay developed. Five independent experiments were performed for each incubating condition.

HPLC analysis

HPLC was performed using the model 126 HPLC pump (Beckman Instruments, San Ramon, CA, USA) with an autosampler model AS-950 (Jasco, Tokyo, Japan).

Separation of atracurium/cisatracurium and laudanosine was carried out on a 5 µ Hypersil C18 column 125×4 mm. The mobile phase concentration was: 30% acetonitrile, 60% Na_2SO_4 24 mmol litre^{-1} in H_2SO_4 5 mmol litre^{-1}, and 10% methanol. The flow rate was 0.6 ml min^{-1}. The fluorometric detector FP-920 (Jasco) was set to 280 nm for excitation and to 320 nm for emission. The lower limit of detection was atracurium or cisatracurium 5 ng ml^{-1} (4 nmol litre^{-1}) and laudanosine 2 ng ml^{-1} (5.6 nmol litre^{-1}). The atracurium isomers (*cis–cis*, *cis–trans*, and *trans–trans*) were identified and separately determined.

Monoquaternary acid, the atracurium metabolite of ester hydrolysis, was not available for us to prepare standard stock solutions for calibration purposes. It could not, therefore, be quantitatively determined. To estimate monoquaternary acid formation, the peak area (as obtained from the HPLC chromatogram) was presented as an arbitrary unit. For the identification of these peaks in the chromatogram, the HPLC chromatogram described by van den Brom[12] was used. As the monoquaternary acid concentration should progressively increase during hydrolysis at low pH (acid hydrolysis), cisatracurium was incubated in HCl solution (pH 3). Increasing peak areas found by subsequent HPLC analysis at 2–8 h intervals during an incubation period of 24 h, confirmed that we were semi-quantitatively measuring monoquaternary acid concentration.

Data analysis

The kinetic model used for data analysis has been described previously.[3] The degradation pathway of the parent compounds (atracurium or cisatracurium) via Hofmann elimination is depicted in Figure 1A. The model includes sequential formation of two laudanosine molecules from one atracurium molecule, with only one molecule of laudanosine being formed in the first step of the degradation of atracurium.

A single rate constant (k_1) defined both the degradation rate of cisatracurium or atracurium and the rate of formation of the first molecule of laudanosine. The second molecule of laudanosine is formed from quaternary monoacrylate, which undergoes further elimination. The corresponding rate constant was designated k_2.

The model was fitted to the time-dependent, measured concentrations of atracurium or cisatracurium and to the sum of both laudanosine molecules in each experiment; the respective half-lives were calculated as $T_{1/2}=\ln(2)/k$. As a parameter for the goodness of fit, the coefficient of determination was used. For the calculations, Scientist software (MicroMath, Salt Lake City, UT, USA) was used.

In our mathematical model, ester hydrolysis, as shown in Figure 1B, was not taken into account by assigning a particular elimination rate constant, as it is not possible to differentiate the individual contribution of Hofmann elimination and ester hydrolysis to the degradation process based

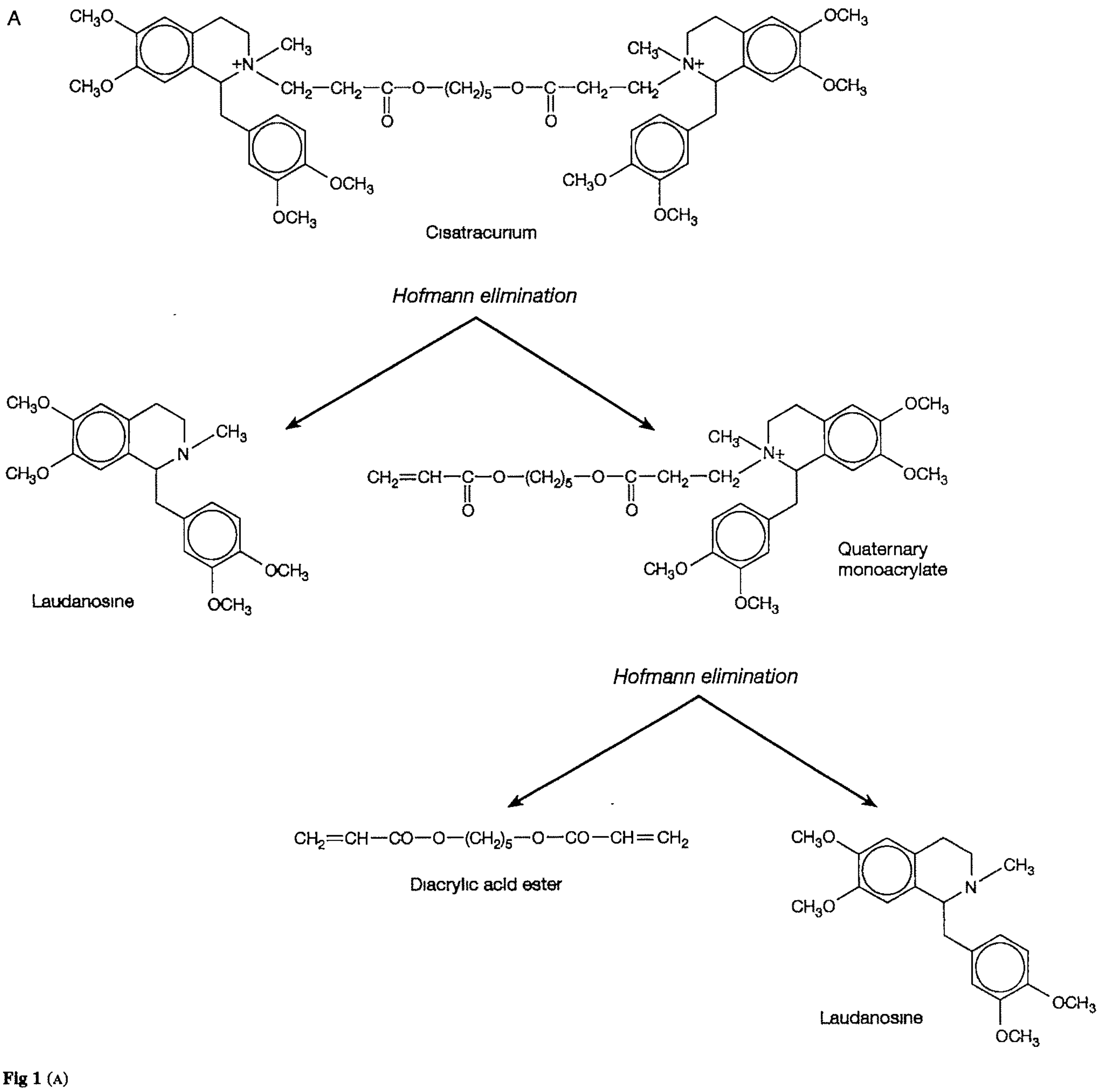

Fig 1 (A)

on the measurement of the concentration of cisatracurium or atracurium and laudanosine. However, in the presence of carboxylesterase, the degradation rate must increase if ester hydrolysis occurs, and detection of the monoquaternary acid metabolite can be considered to be caused by enzymatic ester hydrolysis only.

Results are reported as mean (SD). Statistical evaluation was performed using the *t*-test (df=(10–6)=4). Level of significance was assumed to be 0.05.

Results

The initial concentration of cisatracurium in the incubation solution was 1.80 (0.05) µmol litre^{-1}, that of atracurium was 1.47 (0.07) µmol litre^{-1}, and that of laudanosine was very low (0.056 (0.064) µmol litre^{-1} in cisatracurium solutions and 0.069 (0.033) µmol litre^{-1} in atracurium solutions). The *cis–cis* isomeric group constituted 66.6%, *cis–trans* 28.6%, and *trans–trans* isomers 4.8% of the atracurium mixture.

Results obtained by incubating cisatracurium and atracurium with and without additives at pH 7.4 and 37°C are given in Table 1. The degradation of cisatracurium and atracurium proceeded exponentially in all incubation solutions. The degradation rate was always faster for cisatracurium than for atracurium. The corresponding rate constants (k_1), and the calculated half-lives in the plain solutions and after addition of carboxylesterase, carboxylesterase and BPNP, or BPNP alone are also given in Table 1.

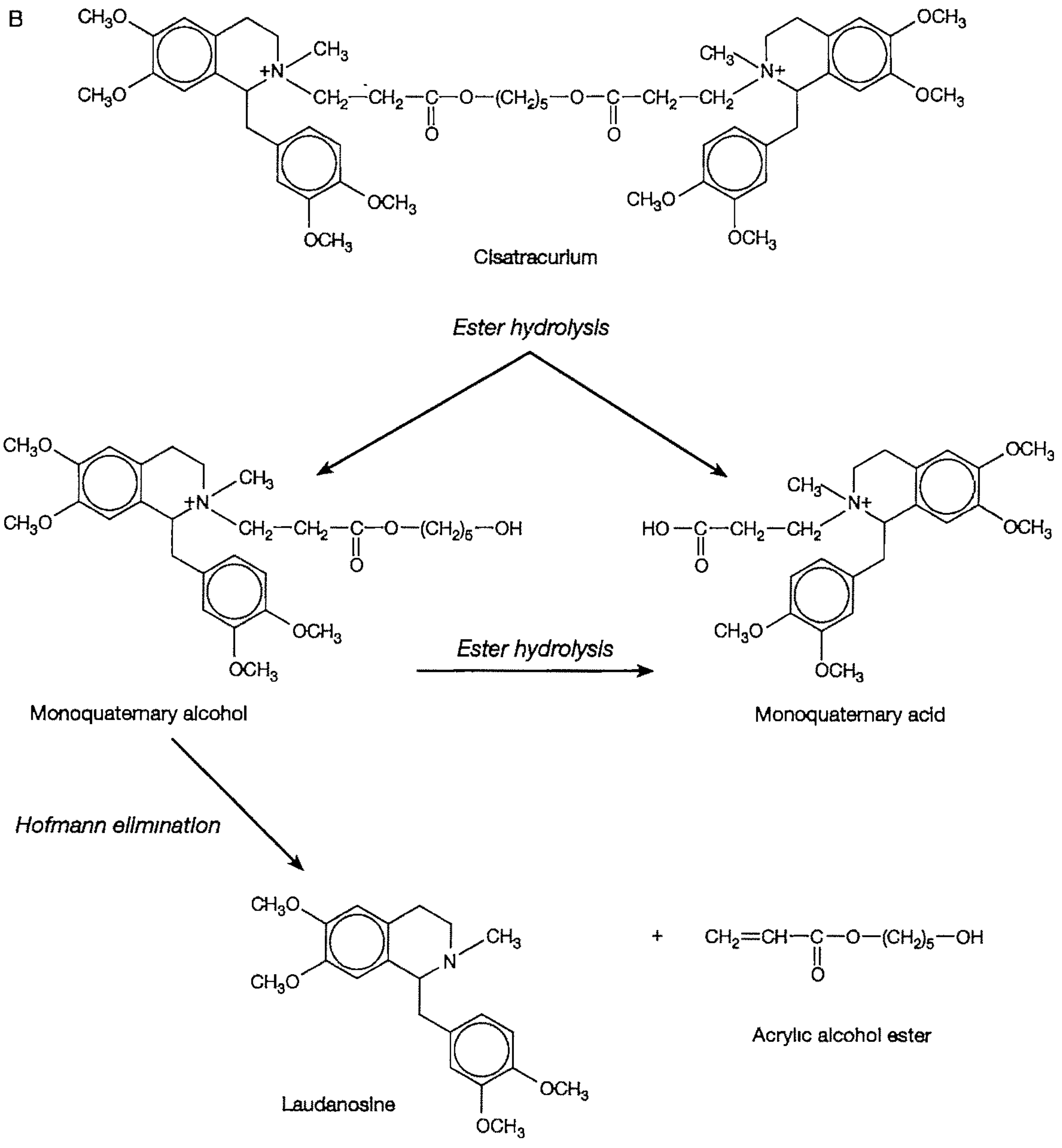

Fig 1 (B)

The proposed model for the degradation of cisatracurium or atracurium and the formation of laudanosine fitted the data well under all experimental conditions.

The half-lives ($T_{1/2}$) of cisatracurium/atracurium in plain phosphate buffer were 33.3 and 39.4 min cisatracurium and atracurium, respectively. After addition of carboxylesterase 20 unit litre^{-1}, no differences in the degradation rate could be found ($T_{1/2}$: cisatr+20CE, 32.7 min; atr+20CE, 43.1 min). An increase in carboxylesterase activity from 20 to 100 unit litre^{-1} did also not affect the degradation rates ($T_{1/2}$:

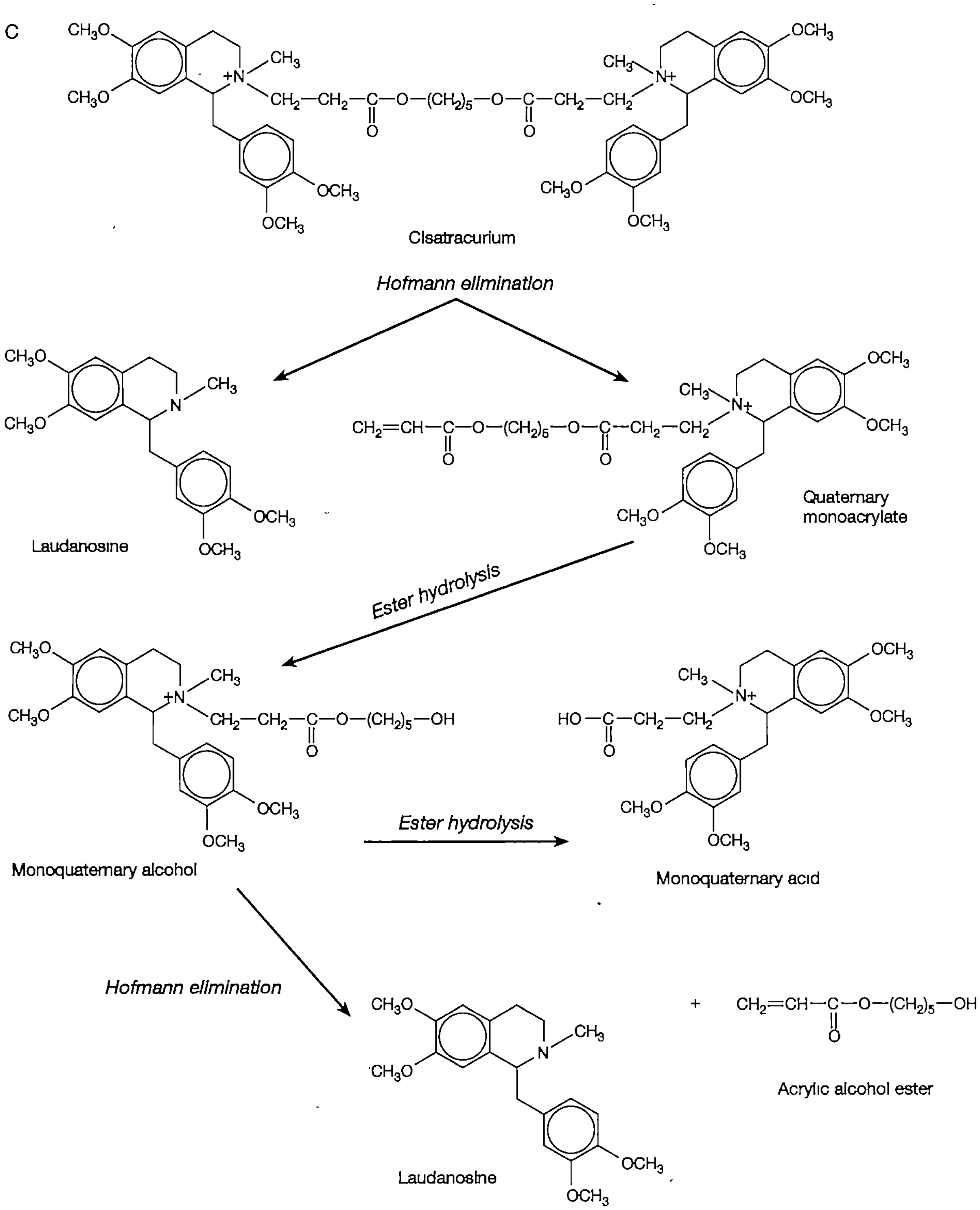

Fig 1 Proposed pathway of cisatracurium degradation (A) Hofmann elimination as the only degradation mechanism (B) Ester hydrolysis as the proposed degradation pathway for the parent drug. (C) Hofmann elimination in the first elimination step, ester hydrolysis for break down of quaternary monoacrylate in the second step. The degradation of atracurium follows the same pathway.

Table 1 Rate constants (mean (SD)) n=5, characterizing the degradation of cisatracurium (cisatr) or atracurium (atr) and the formation of the first molecule of laudanosine (k_1) in plain phosphate buffer and after addition of carboxylesterase (CE), carboxylesterase and esterase inhibitor BPNP, or BPNP k_2, rate constant for the formation of the second molecule of laudanosine $T_{1/2}$, half-lives calculated for the rate constants k_1 C1 and A1, cisatr/atr in plain phosphate buffer C2/C3 and A2/A3, cisatr/atr after addition of carboxylesterase 20 or 100 unit litre^{-1}. C4/C5 and A4/A5, combined addition of carboxylesterase 20 unit litre^{-1} and BPNP 10 μmol litre^{-1} or carboxylesterase 100 unit litre^{-1} and BPNP 50 μmol litre^{-1}. C6 and A6, cisatr/atr after addition of BPNP 10 μmol litre^{-1} P values k_1 was compared in group C1 or A1 (cisatr/atr in phosphate buffer) with groups C2–C6 and A2–A6, respectively P values for k_1 C2 *vs* C3, 0 135, C4 *vs* C5, 0 635, A2 *vs* A3, 0.213, A4 *vs* A5, 0 180

Incubating solution	k_1 (min^{-1})	$T_{1/2}$ (min)	k_2 (min^{-1})	Coefficient of determination	P value
Cisatracurium					
C1 (cisatr)	0.0208 (0 0009)	33.3	0 0037	0.9925	
C2 (cisatr+20CE)	0.0212 (0 0012)	32.7	0 0330	0.9876	0 803
C3 (cisatr+100CE)	0 0185 (0.0008)	37.5	0.0013	0.9941	0.129
C4 (cisatr+20CE+10BPNP)	0 0214 (0 0029)	32.4	0.0042	0 9703	0.853
C5 (cisatr+100CE+50BPNP)	0 0194 (0.0026)	35.7	0 0052	0.9847	0 638
C6 (cisatr+10BPNP)	0.0214 (0 0011)	32 4	0 0039	0.9907	0.695
Atracurium A1 (atr)	0 0176 (0 0007)	39 4	0 3549	0 9968	
A2 (atr+20CE)	0 0161 (0 0005)	43 1	0 5591	0 9977	0 156
A3 (atr+100CE)	0.0183 (0.0014)	37 9	0.0136	0 9923	0.678
A4 (atr+20CE+10BPNP)	0.0181 (0.0016)	38 3	0.0813	0.9905	0 789
A5 (atr+100CE+50BPNP)	0 0152 (0.0008)	45 6	0 0695	0 9963	0.087
A6 (atr+10BPNP)	0 0189 (0.0013)	36 7	0.0220	0.9952	0 428

cisatr+100CE, 37.5 min; atr+100CE, 37.9 min), or the concentration of monoquaternary acid. The addition of the esterase inhibitor BPNP did not change the half-lives ($T_{1/2}$: cisatr+20CE+10BPNP, 32.4 min; cisatr+100CE+50BPNP, 35.7 min; atr+20CE+10BPNP, 38.3 min; atr+100CE+50BPNP, 45.6 min) nor the areas under the monoquaternary acid peaks. Control measurements with BPNP showed only marginal differences in degradation ($T_{1/2}$: cisatr+10BPNP, 32.4 min; atr+10BPNP, 36.7 min).

As a representative example for the time course of degradation, the concentrations of cisatracurium and laudanosine in phosphate buffer without and with the addition of carboxylesterase 20 unit litre^{-1} are illustrated in Figure 2A. No differences in the respective degradation rates were apparent.

Those peak areas of the chromatogram that were assumed to represent the monoquaternary acid, increased rapidly during incubation in the presence of esterase. The time course, indicative of the change in concentration of this metabolite, is shown in Figure 2B. After an initial increase during the first 60 min of incubation, the concentration of the metabolite slowly decreased. In the absence of carboxylesterase, no change in monoquaternary acid concentration could be detected.

Discussion

In vitro investigations in various buffers and plasma[4 6 8 9] suggest that cisatracurium and atracurium undergo temperature and pH-dependent Hofmann elimination forming laudanosine and a quaternary monoacrylate (Fig. 1A). In the second degradation step, another molecule of laudanosine and a molecule of diacrylic acid ester are produced from quaternary monoacrylate. The degradation rates determined *in vitro* and *in vivo* were reported to differ significantly. Tsui and co-workers[8] found a half-life for a mixture of the *cis–cis* isomers in humans of 20.5 min; but using atracurium, Stiller and co-workers[4] found a half-life of 58 min for atracurium in Sörensen buffer, compared with 21 min in plasma.

The role of ester hydrolysis and its relevance to the *in vivo* elimination process have not been extensively studied. Welch and co-workers[9] reported the degradation rate of cisatracurium in Sörensen buffer to be similar in the presence or absence of a non-specific plasma esterase. Nevertheless, the different elimination rates found in *in vivo* and *in vitro* experiments have been interpreted by several authors to be the result of ester hydrolysis.[4 7 11] Esterase can promote the ester hydrolysis of the parent molecule to produce monoquaternary alcohol and monoquaternary acid (Fig. 1B). Monoquaternary alcohol then undergoes further Hofmann degradation to form laudanosine. But, if the parent molecule (cisatracurium/atracurium) is degraded primarily by Hofmann elimination, then the esterase would break down the resulting quaternary monoacrylate (Fig. 1C), forming monoquaternary alcohol, which is an unstable molecule and would be further degraded by ester hydrolysis to the more stable monoquaternary acid.[9]

In our mathematical model for the degradation of cisatracurium/atracurium and the generation of laudanosine, the first rate constant k_1 was calculated from the measured concentrations of the parent drug. Accordingly, the rate constant k_1 is a reliable estimate for the generation of the first molecule of laudanosine. Analysing the role of ester hydrolysis in the context of the suggested degradation pathways (Fig. 1B and C), by the addition of carboxylesterase, the rate constant k_1 should increase if ester hydrolysis splits cisatracurium or atracurium to a significant degree (Fig. 1B). If ester hydrolysis occurs only in the second step

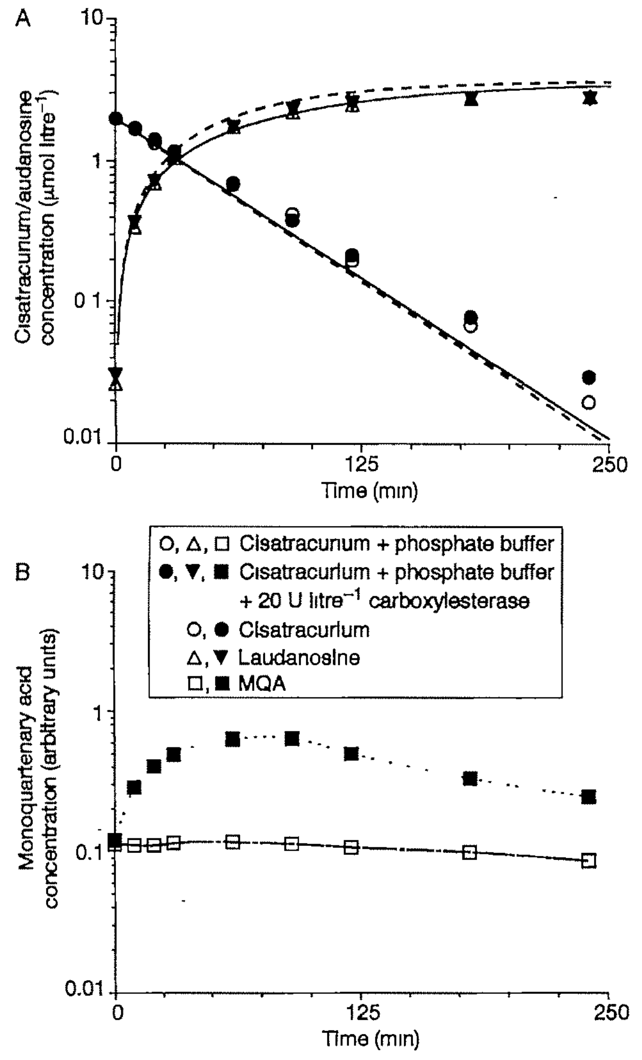

Fig 2 Time course of cisatracurium degradation and formation of laudanosine (A), and formation of monoquaternary acid (B) (A) Continuous and dashed lines show the decay of cisatracurium and formation of laudanosine as calculated from the model (B) The dashed and dotted lines show time course of monoquaternary acid concentration and were fitted using a spline function. Note that concentration of monoquaternary acid is given in arbitrary units. Data shown represent the means of the corresponding concentration of each group

of degradation (splitting of quaternary monoacrylate, Fig. 1C), k_1 would not change, whereas the formation rate of the second laudanosine molecule, k_2, should.

As only the total concentrations of laudanosine can be measured, the calculated rate k_2 of the formation of the second laudanosine molecule must be considered an approximation. We did not therefore use k_2 as a quantitative measure in characterizing the role of ester hydrolysis. However, this degradation pathway does evidently exist because the monoquaternary acid concentration increased in the presence of carboxylesterase (Fig. 2B).

Our experiments did not yield a significant change in the rate constant for the elimination of cisatracurium/atracurium (Table 1) or in the concentrations of monoquaternary acid, with either carboxylesterase 20 or 100 unit litre^{-1} added to the incubation solution. This result suggests a negligible contribution of ester hydrolysis to the degradation of cisatracurium/atracurium and evidently confirms the degradation pathway schematically shown in Figure 1C.

The peaks representing monoquaternary alcohol did not change during incubation of cisatracurium/atracurium (data not shown). These results correspond with the assumption of Welch and co-workers[9] that monoquaternary alcohol converted rapidly to the more stable monoquaternary acid and laudanosine, and also that a certain amount of ester hydrolysis must be involved in the second stage of atracurium degradation in human plasma.[9]

The degradation rate of atracurium proved to be somewhat slower than that of cisatracurium (Table 1). Atracurium is a mixture of 10 stereoisomers differing in their respective degradation rates. Tsui and co-workers[8] showed that *in vitro* degradation of the *cis–cis* isomers (representing about 67% of the atracurium isomers) occurred somewhat faster ($T_{1/2}$=57 min) than that of the *cis–trans* ($T_{1/2}$=60 min) and *trans–trans* isomers ($T_{1/2}$=66 min). Therefore, atracurium (containing about 14% cisatracurium) is to be expected to degrade more slowly than cisatracurium *in vitro*.

As reported previously,[3] the *in vitro* degradation rate of atracurium via Hofmann elimination strongly depends on the ion composition and ion concentrations of the incubation buffers used, and this fact alone may well explain the observed differences between the degradation rates of atracurium *in vivo* and *in vitro*. Our present results strongly support this suggestion, as they clearly show that ester hydrolysis does not play a major role in the degradation of atracurium.

Species-specific differences in the relative roles and activities of esterases are known to exist.[11] In the rat, Welch and co-workers[9] reported that ester hydrolysis played a major role in the decomposition pathway of atracurium (Fig. 1B). However, in respect of the enzymatic breakdown of cisatracurium and atracurium, it should be emphasized that the results obtained from animal experiments must not be extrapolated to humans.

In conclusion, our data suggest a measurable, but minimal role of ester hydrolysis in the degradation process of cisatracurium and atracurium. Its clinical relevance has to be discussed with caution, as the potential involvement and yet unknown contribution of nucleophilic substances like acetylcysteine[13] in the degradation of neuromuscular blockers have yet to be investigated.

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BJA

REVIEW ARTICLE

Chirality: a blueprint for the future

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Chirality is a fundamental characteristic of nature and pervades the living world. We have been under its constant influence throughout evolution as a result of the asymmetrical nature of the environment and, while the origin of this phenomenon is a matter of speculation, the evidence surrounds us all. Most proteins, for example, are formed of L-amino acids while carbohydrates are composed of natural sugars, all D-isomers. Biological receptor systems comprise a complex structural organization of helices and sheets and display 'handedness'. This results in a profound effect on drug–receptor interactions.

The subject has fascinated scientists since the middle of the 19th century, when Louis Pasteur[65] first demonstrated the stereoisomeric forms of tartaric acid. Following earlier work by de la Provostaye, he undertook crystallographic studies on tartaric acid and its salts, and demonstrated the presence of hemihedral facets. In some instances, these were orientated to the left and in others to the right. By handpicking the crystals, he divided them into two groups and found that the solutions rotated light in equal but opposite directions. Pasteur recognized that the cause of this phenomenon lay in the molecular structure, and by extending these ideas he evolved the theory of the asymmetrical carbon atom.

Why is chirality relevant to anaesthesia? Advances in chiral technology are allowing the commercial synthesis of single-isomer compounds hitherto of academic interest only. By understanding the role of these stereoisomers in biological systems, the next logical step is the application of this knowledge to human physiology and pharmacology.

In addition, incentives have been provided by the drug regulatory authorities, who realize the potential benefits of single-isomer compounds in terms of simplification of the pharmacological profile and an elimination of so-called isomeric ballast.

International Union of Pure and Applied Chemistry (IUPAC) terminology

Isomers are unique molecular entities composed of the same molecular constituents with common structural characteristics. Stereoisomers are isomers whose atoms, or groups of atoms, differ with regard to spatial arrangement of the ligands, and they can be either geometrical or optical isomers. Geometrical isomers are stereoisomers without optically active centres and result from restricted rotation as a result of the presence of, for example, a carbon–carbon double bond (e.g. *cis*-2-butene, *trans*-2-butene). Geometrical isomers are not mirror images of one another. For these compounds, terminology such as *cis* (meaning 'together' or 'same side') and *trans* (meaning 'opposite side') are used to describe the spatial arrangement. Optical isomers are a subset of isomers that are optically active and are said to possess a 'chiral centre'. This term derives from the Greek *chiros*, meaning 'handed', and describes a molecule that is not superimposable on its mirror image. This is the necessary and sufficient definition for a molecule to be described as chiral. The majority of this review focuses on optical isomers, as the separation of geometric isomers is well established.

Optical isomerism can arise in a number of ways, but in its most familiar form a central carbon or sulphur atom is attached to four different groups, thus producing a tetrahedron. Van't Hoff first proposed this concept in 1874 and suggested that the four valencies of a carbon atom are directed towards the corners of a regular tetrahedron, thus enabling the concept of asymmetry to be realized (Fig. 1).

Optical isomerism enables the existence of two non-superimposable mirror images or enantiomers (Greek *enantios*=opposite, *meros*=part) that share identical physi-

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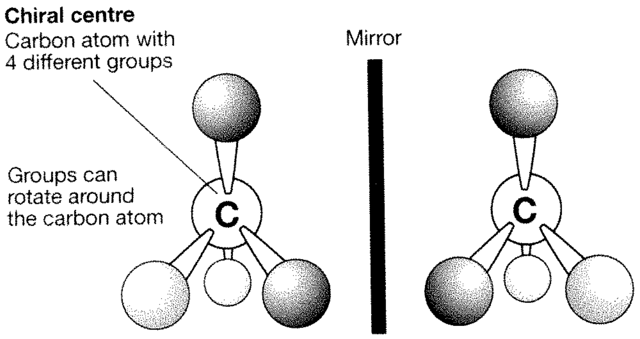
Chiral centre
Carbon atom with 4 different groups
Mirror
Groups can rotate around the carbon atom
C
C

Fig 1 General depiction of a molecule with a chiral centre and its enantiomers.

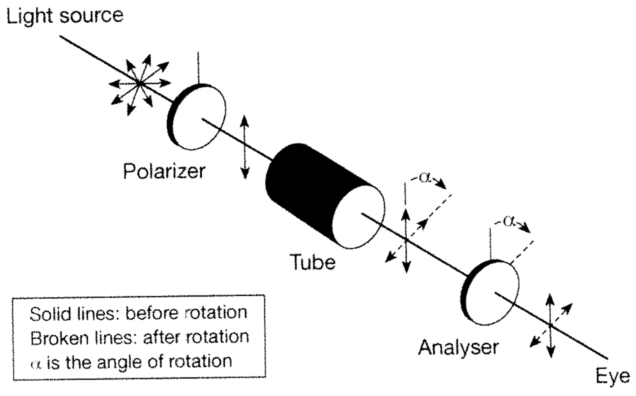
Light source
Polarizer
Tube
-α
-α
Analyser
Eye
Solid lines: before rotation
Broken lines: after rotation
α is the angle of rotation

Fig 2 Measurement of optical activity using a polarimeter.

cochemical properties but differ in their rotation of plane-polarized light. Importantly, they can also differ in pharmacological profile, owing to highly stereospecific interactions at the receptor interface. A mixture of two enantiomers is called a 'racemate', a term popularized by Beilstein. A racemate is designated by the prefix (±) or rac-, or by the symbol RS or SR, and has no optical activity. The use of the term 'racemic mixture' is to be discouraged as it has been used as a synonym for both 'racemate' and 'racemic conglomerate'.

The nomenclature of chiral compounds has been clarified by the adoption of the International Union of Pure and Applied Chemistry (IUPAC) Recommendations 1996, which apply to basic terminology in stereochemistry.[42] Chiral compounds can be described by a combination of terms.

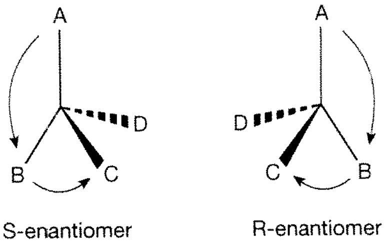

Fig 3 Sequence rule notation. Bonds represented as solid lines are in the plane of the paper, those drawn with dotted lines project away, and those represented by a wedge project towards the reader. Group priority (atomic size) is indicated as A>B>C>D, A representing the largest size. With the group of lowest priority projected away from the reader, the sequence is anticlockwise (S) in the enantiomer on the left and clockwise (R) in the enantiomer on the right.

Relative descriptors

The most common way to refer to the chirality of a molecule is still based on the effect it has on the rotation of optical light, with the descriptors (+) and (–) applied when the rotation is clockwise and anticlockwise respectively (Fig. 2). Isomers that rotate light clockwise and anticlockwise are termed 'dextrorotatory' and 'laevorotatory' respectively.

Optical rotation, although an unambiguous physical property, varies with measurement conditions and these are therefore standardized. The degree of rotation is measured at the sodium D line at 254 nm, as rotation varies with frequency. The actual property measured is an electronic transition between the orbitals in the molecule under study. The complete spectrum, the circular dichroism (CD) spectrum, differs from the ultraviolet spectrum in being both positive and negative. Rotation is determined by both electronic and magnetic moments. Achiral molecules, which have no magnetic moment, do not rotate plane-polarized light.

At very low rotation strengths, errors can occur as a result of the presence of contaminants. The type of solvent used and pH changes can also produce dramatic changes in the CD spectrum.

Absolute descriptors

The sequence rule notation, proposed by Cahn and colleagues, [12] is based on attaching an order of priority to substituent ligands attached to the central chiral atom. In this model, the ligands around the chiral centre are 'sized' according to their atomic number, placing the smallest to the back and looking at the remainder in terms of relative size (Fig. 3).

Consider a molecule Cabcd, where a, b, c and d are groups placed around a central atom C. If the sequence of the ligands in terms of size (largest to smallest) produces a clockwise progression, the arrangement is termed 'R' from the Latin *rectus* (right). Conversely, an anticlockwise order is termed 'S' from the Latin *sinister* (left). Any chiral molecule can be designated in this way. If two or more ligands are of equal size, the next atom along the chain is examined. Thus, a full description of a chiral compound may be given by an expression combining terms for the absolute descriptor, the relative descriptor and the chemical or generic name, e.g. S(–)bupivacaine.

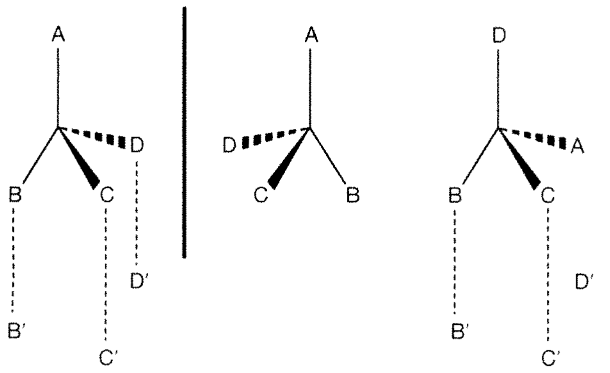

Fig 4 Easson–Stedman model. Enantiomeric interaction with a chiral biological macromolecule. The enantiomer on the left is involved in three simultaneous bonding interactions at the receptor, whereas that on the right interacts at two sites only. A, B, C and D represent ligands on the chiral compound and A′, B′, C′ and D′ are corresponding sites on the receptor.

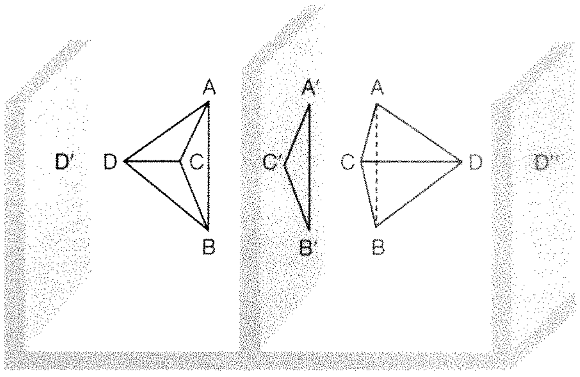

Fig 5 The four-location model. This is a four-point location model of the stereoselectivity of a protein. Groups A, B and C of different isomers occupy the same protein locations (A′, B′ and C′), whereas the D groups, which point in opposite directions, interact at different positions (D′ and D″).

Stereospecific biological interactions

Interaction of a drug with a biological system produces a cascade of events that ultimately leads to a point at which some physiological response can be measured. The initial interaction is highly stereospecific and a hypothesis to explain this was proposed by Easson and Stedman in 1933 (Fig. 4).[20] These authors adhered to the general principle that any three-dimensional molecule can be represented topologically by the simplest polyhedron, a tetrahedron. Attachment of the drug to the receptor was analogous to the 'attachment of a glove to the hand'. Maximal interaction in this model is derived from Aa+Bb+Cc+Dd. The interaction with the opposite enantiomer can be considered in a similar way, but here there are fewer congruencies at the binding site. The more each of the interactions tends to the maximum, the greater the separation in affinity between the enantiomers (Pfeiffer's rule).[67]

When comparing affinities, the enantiomer with the highest affinity is termed the 'eutomer' and that with the lowest affinity the 'distomer'. The pharmacological activity of the two enantiomers can therefore be compared by calculation of the 'eudismic ratio'. Eudismic analysis provides a powerful tool for drug design, by optimizing a series of enantiomer pairs by the comparison of the eutomers and distomers in a series of analogues. By providing a description of the increasing potency of the molecule as the affinity of the enantiomer with a receptor increases, a series of compounds can be analysed and information provided for molecular design. There can potentially be more than one eudismic ratio for a racemate if the compound has more than one pharmacological effect.

Recently, Mesecar and Koshland[61] have proposed a new 'four-location' model to account for stereospecificity (Fig. 5). The three-point attachment model described previously holds only if it assumed that the ligand can approach a flat protein surface from the top. If the binding sites on the protein molecule are in a cleft or on protruding residues, the three-point model will not be sufficient to allow discrimination. It is therefore suggested that a fourth point, whether a binding site or a location, is essential in order to distinguish between enantiomers in an actual protein structure.

To illustrate this, the enzyme isocitrate dehydrogenase (IDH) was used as an example. Its crystalline structure was examined using electron density mapping in the presence and absence of Mg^{2+}. When metal-free crystals of IDH were presented with rac-IDH, only the L isomer bound to the active site. In contrast, in the presence of Mg^{2+}, only the D isomer was seen at this site. A fourth group, the hydroxyl of the C-2 atom, varied its association according to conditions and accounts for the difference. The conclusion was that a minimum of four designated locations is needed in order to explain a protein's ability to discriminate between enantiomers.

Drug development

Until recently, the majority of single-isomer drugs available were those derived from natural sources (e.g. morphine, epinephrine, hyoscine), and racemates predominated. There is now clear evidence of a trend in the pharmaceutical industry towards the development of chiral drugs, either *de novo* or by deriving them from racemates marketed previously (i.e. 'chiral switching').[77] Several factors have influenced this trend, which has occurred independently and in parallel with a quest in the industry as a whole to develop more potent, selective and specific drugs. Chiral switching is a small component of this trend and relies on the existence of a racemate in the first place. The process is equivalent to developing a new active substance and requires a new application, but data on the racemate may be used as appropriate, together with 'bridging studies'. There is, however, limited potential in the market for the degree of

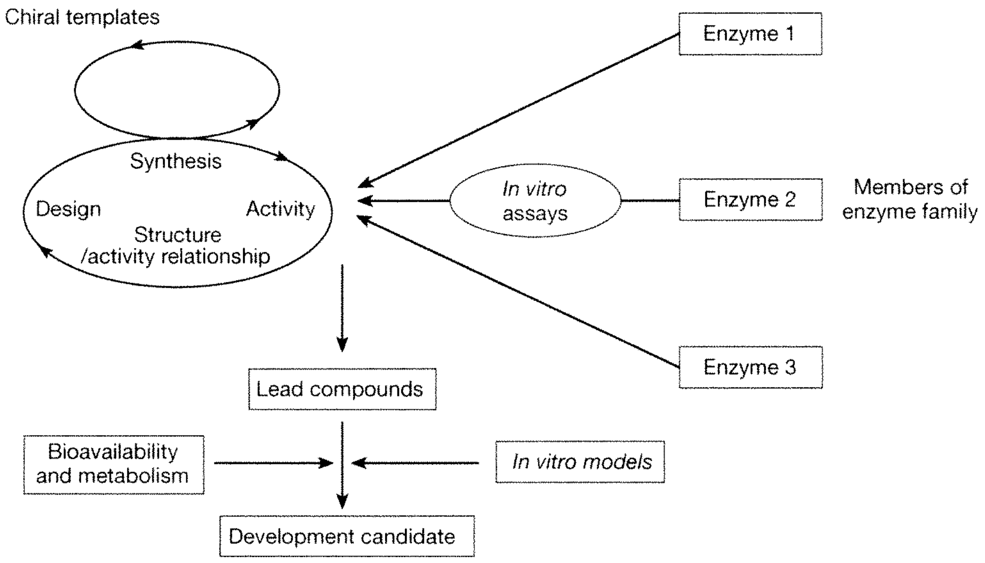

Fig 6 Chiral technologies to produce new drug candidates.

therapeutic benefit obtained to justify the degree of investment.

The real benefit of chiral technology lies in its application in the search for novel chemical entities. Regarding enantiomers as chemically distinct entities at an early stage in the research and development process is a valuable aid in the understanding of drug mechanisms. The key targets of selectivity and specificity can be pursued in an effort to improve drug efficacy while minimizing toxicity. Rational drug design (based on increased understanding of biological receptor systems) combined with chiral technology allows a 'chiral template' to be developed, as illustrated in Figure 6.

Coinciding with this has been the awakening of the drug regulatory authorities to the different pharmacological and toxicological profiles of enantiomers. The FDA policy statement for the development of stereoisomeric drugs, issued in 1992, made it more difficult to obtain approval for racemates.[25] This statement made it clear that approval could not be granted for a drug containing more than one isomer unless the pharmacokinetic and pharmacodynamic properties of each could be described and, more importantly, justified. In addition, the FDA offers a shortened approval process for the enantiomeric versions of approved drugs, with the promise of patent protection.

Drug regulatory authorities in other countries have followed this lead. Additional isomers in a compound are no longer considered as 'silent passengers' but as potential contaminants (so-called isomeric ballast). While it is unlikely that many racemates will be approved in future as a result of this, there are still situations in which their production is justified. These include situations in which (i) the enantiomers are configurationally unstable *in vitro* or undergo racemization *in vivo*; (ii) the enantiomers have similar pharmacokinetic, pharmacodynamic and toxicological properties; and (iii) it is not technically feasible to separate the enantiomers in sufficient quantity and/or quality.

Situations also exist in which an enantiomeric ratio other than unity may be justified if the ratio is expected to improve the therapeutic profile, as there is no reason to expect the optimum eudismic ratio to be necessarily 1:1 (i.e. the dose–response curves would not usually be expected to be congruent).

Methods of enantioselective synthesis

More than 50% of commercial drugs have at least one stereogenic centre. Research efforts since the mid-1980s have succeeded in producing a range of chiral technologies that aim to exert ultimate control over a chemical reaction by diverting its enantioselectivity. Indeed, where this is not the case, synthetic production of a racemate necessarily yields less than 50% of the desired drug. The reliable preparation of chiral molecules of very high enantiomeric purity therefore allows both biological evaluation and industrial application.

The key methods for the production of single-isomer drugs are described below.

Isomer separation

This falls into three main categories.

Separation by chromatography

Chromatography is the only method applicable to all stages of the pharmaceutical development chain from discovery to the full-scale process.

The first application of a countercurrent chromatographic process, of which the simulated moving bed (SMB) is an example, was based on Broughton's patent from 1961 and was widely adopted in the petrochemical industry. Since the 1990s, the problems of scaling down the multi-ton systems used in this industry have been overcome, enabling laboratory-scale systems to be developed for application to medicinal chemistry.

The basic concept of SMB technology is the continuous countercurrent movement of stationary and mobile phases in which the movement of a stationary phase is simulated. The small particles in this component are packed into single columns and connected to form a circle. Four external valves allow the addition and subtraction of feed and effluent. The mobile phase is pumped through the circle and when it passes the stationary phase a slight separation occurs, the less absorbable compound running in front and the more absorbable compound staying behind. When steady state is reached, the system can be operated continuously. An example of a pharmaceutical compound separated by SMB chromatography is tramadol.

Crystallization

Two methods predominate. First, the racemic product or a simple chiral salt of the product (e.g. hydrochloride) may, under specific conditions, crystallize to give only one isomer. This method has been used in the resolution of α-methyl-L-dopa, methadone, asparagine and glutamic acid. These compounds are known as conglomerates; however, relatively few compounds (about 7%) exhibit this behaviour. The second crystallization method is to form a diastereomeric salt by mixing the racemate with a chirally pure compound. Again, under the correct conditions, only one diastereomer will crystallize out. This technique relies upon the ability of the two components to form a salt; however, a covalent bond could also be formed with a chiral auxiliary. This last example is not widely used (if at all) in the manufacture of chiral drugs.

Enzymic resolution (biotransformation)

Enzyme-mediated reactions are appealing to the developmental chemist as they produce a diverse range of transformations and avoid extreme reaction conditions with their concomitant inflated manufacturing costs and potential hazards. Enzymes have been used not only in the resolution of racemates but also to allow the introduction of new stereogenic centres. Their use for the preparation of chiral pharmaceuticals has increased only recently as the methods employed have been adapted to commercial production. Enzyme resolution allows the separation of a racemic drug or drug derivative (e.g. an ester) into its two enantiomers owing to the fact that the enzyme only reacts with one isomer. Two general approaches are used. The first involves incorporating in the synthetic design of the desired compound an enzyme resolution stage as a means of separating and recovering the isomer. Alternatively, the diversity of biotransformations that enzymes can produce is considered and synthesis is designed around that transformation which results in the desired chiral centre(s).

As the use of enzyme transformations in the pharmaceutical process expands, these two approaches may ultimately converge in the creation of the desired product. Enzymatic resolution has been used in the preparation of benzodiazepines, e.g. S-14 lotrafiban (Smith Kline Beecham), antibacterial drugs, e.g. levofoxacin, and antiinflammatory drugs, e.g. the S isomers of 2-aryl propionic acids [S-naproxen, S-suprofen].

Asymmetrical synthesis

This term refers to the process of taking an achiral drug (i.e. one containing no chiral centre) and synthetically converting it by one of a number of routes to one isomer of a compound with a chiral centre. These methods include asymmetrical hydrogenation (asymmetrical catalysis), asymmetrical dihydroxylation and hydroxamination etc. Computational toolkits for molecular design, visualization and analysis (e.g. SYBYL, created by Astra-Zeneca) can assist the process.

Chiral pools

The term 'chiral pool' refers to the many naturally available chiral molecules that exist in high enantiomeric purity and frequently at low cost. The most versatile chiral starting materials, in order of their industrial production per annum, are: carbohydrates, α-amino acids, terpenes, hydroxy acids and alkaloids. Other inexpensive chiral natural products are ascorbic acid, dextrose, ephedrine, limonene, quinidine and quinine, etc. Naturally occurring amino acids are readily available from bulk fermentation processes and these constitute the most important class within the chiral pool, with amounts available ranging from 10 to 10^5 tons per year. These compounds can be incorporated into the molecule to provide the desired chiral centre (e.g. synthetic peptides) or to induce the desired chiral centre during synthesis (chiral induction or diastereoselective synthesis). The term 'diastereoselective synthesis' refers to the formation of a new chiral centre into a single enantiomer when only one new isomer is formed. Chiral starting materials such as amino acids can be converted into antibacterials, cytotoxic agents and protease inhibitors (e.g. ritonavir) using this technology.

Overall, it is evident that tremendous advances have been made over the last few years in the utilization of modern asymmetrical synthetic tools that enable single-isomer drugs to be brought to commercial fruition.[43]

Practical example

The manufacture of ropivacaine.HCl.H_2O provides an example.[26] The technique is based on a resolution method published by Tullar[78] some 30 yr ago, when it was found that (±)-2′,6′-pipecoloxylide could be resolved by the use of (–)-dibenzoyl-L-tartaric acid (a natural isomer), thereby making virtually any member of the series of *N*-substituted enantiomeric derivatives available via a subsequent alkylation step. Ropivacaine.HCl.H_2O can be synthesized in three steps. (i) *Resolution* is achieved by fractional crystallization.

Optical purity and enantiomeric yield are dependent on both the crystallization time and the water content of the solvent. (ii) *Alkylation*: *N*-alkylation of the resolved pipecoloxylidide base is then performed and the HCl salt precipitated from the organic phase by adding hydrochloric acid. (iii) *Final optical purification*: final recrystallization of the crude hydrochloride from acetone/water (10:1) gives ropivacaine.HCl.H_2O. This process generates an overall yield of 50% and an optical purity of >99.5%.

Metabolite switches

There is currently much interest in the metabolites of known drugs as well as in their enantiomers.[77] The ability to produce the active metabolic moiety directly may simplify pharmacogenetic and other issues, and a variety of drugs are under investigation. These include the prokinetic agent cisapride (active metabolite norcisapride) and the antimalarial halofantrine (active metabolite desbutylhalofantrine). Desmethylzopiclone has also been studied; this is a metabolite of zopiclone in which an *N*-methylpiperazine ring has been demethylated.

Pharmacokinetics

The processes of absorption, distribution and metabolism are critical determinants of drug action and can assume equal relevance to the actual biological effect of the drug at its receptor site. The potential for discrimination between enantiomers at each of these stages is therefore important and highlights the need for stereospecific drug assays.

After administration of a racemate, the proportion of enantiomers (initially 1:1) changes continuously until a new steady state is reached. Significant differences may be seen in the rates of enzymatic conversion, carrier transport, protein binding, distribution and elimination, i.e. active processes. Passive processes, determined primarily by physicochemical characteristics, show smaller differences. The eudismic ratio thus changes constantly and is subjected to the confounding influences of genetic polymorphism and chiral inversion. Toxic side-effects may reside not in the parent isomer but in an isomer-specific metabolite.

It is therefore clear that pharmacokinetic data paying no heed to these features and simply extrapolated from multicompartmental modelling is at best misleading, and has been denigrated by Ariens as 'pseudoscientific nonsense'.[6] Ideally, analytical techniques allowing quantitative *in vivo* sampling should be developed and validated at an early stage of drug development. Some of the techniques used for this purpose include chiral high-performance liquid chromatography, chiral gas chromatography, nuclear magnetic resonance, optical rotatory dispersion and X-ray crystallography. Examples of how pharmacokinetic processes may be influenced by enantioselectivity are discussed below.

Absorption

Passive transfer across cellular membranes is dominated by lipophilicity and the extent of ionization at physiological pH. There is generally little enantiomer-specific difference as the lipid and aqueous solubilities are identical.

Active transport processes can discriminate between the enantiomers, with implications for bioavailability. For example, the inherent vasoconstriction characteristic of the S(–) isomer local anaesthetics results in the drug remaining at the site of injection longer and may influence the peak plasma concentration.[4]

Protein binding

Most drugs bind to plasma proteins to a varying degree. Stereoselectivity in binding can have a significant effect on the amount of drug in the plasma and this is species-dependent. Albumin is the most predominant plasma protein and dominates binding for acidic drugs, while α_1-acid glycoprotein (AGP), present to the extent of 3% of albumin, has a lesser overall effect. However, the elevation in AGP seen in acute illness increases the amount of drug bound to it. Variations in protein binding between enantiomers can offset their potency difference. A case in point is warfarin, in which the S(–) enantiomer is two to five times more potent than the R(+) enantiomer, but this is negated to a large extent by the greater plasma clearance of the former.[11]

Metabolism

Enzyme systems reliant on receptor–drug interactions are subject to stereoselective influences in a similar manner to other systems. The interactions between enantiomers can be complex, existing both within the species (i.e. pharmacogenetic differences) and transcending it. Extra complications arise as a result of inversion processes, whereby one enantiomer is converted into another. Processes such as these, which alter the eudismic ratio, can have toxicological implications, and it is equally important to realize that toxicity may not reside in the parent isomer but in an isomer-specific metabolite. Competition between enantiomers can also occur when more than one metabolic pathway for substrate breakdown exists, stereoselective factors determining which pathway is followed. Age, race, sex and disease all complicate the issue.

Chiral synthesis and its impact on anaesthetic practice

General anaesthetic agents

Inhalational agents

The majority of the inhalational anaesthetics used currently are chiral, with the notable exception of sevoflurane. Exploitation of stereochemical technological processes

Table 1 Relative potencies of anaesthetic isomers. ED_{50}=median effective dose; MAC=minimum alveolar concentration, EEG=electroencephalogram

		Isomer	
		S	**R**
Isoflurane			
Pond snail K^+ ion channel[16]	Ion channel current generation	S twice as effective as R	
Mouse, *in vivo*[70]	Sleep time (min)	9	6
Rat, *in vivo*[17]	MAC	1 06	1.62
Rat, *in vivo*[24]	MAC	1 44	1.69
Thiopental			
Animal[28]	EEG depression (% baseline)	10	40
Human $GABA_A$[32]	ED_{50} (μM)	26	52
Etomidate			
Tadpole[34]	ED50 (μM)	57	3 4

may allow potential clinical benefits to be achieved while simultaneously promoting a greater understanding of their mechanism of action. Recent work attempting to elucidate the mechanism of action of anaesthetic agents emphasizes the importance of specificity in action, whereas the more generalized earlier theories were based on physical characteristics such as lipid solubility. A difference in potency between the isomers of an inhalational anaesthetic agent would therefore lend support to specific anaesthetic–protein binding interactions.

Franks and Lieb[27] studied the effects of isomers of isoflurane on nerve ion channels derived from the pond snail and found the S(+) isomer to be twice as potent in triggering an anaesthetic activated potassium current as the R(–) enantiomer. Harris and colleagues[34] conducted *in vivo* studies and gave mice intraperitoneal injections of the isomers of isoflurane. They found a greater sleep time with the S(+) isomer. Similar evidence for greater potency of the S(+) isomer of isoflurane was demonstrated in the rat model by Lysko and colleagues.[53] The minimum alveolar concentration (MAC) of S(+)-isoflurane was 1.06 (SD 0.07)% compared with 1.62 (0.02)% for R(–)-isoflurane and 1.32 (0.03)% for the racemate. This was the first study to look at the stereoisomers of a volatile agent when given by a conventional route (inhalation) and to measure a clinically relevant outcome (MAC). While some groups have supported these findings,[34 35 62 64] there have been conflicting results.[31 46 63] In a repetition of the study of Lysko and colleagues, Eger and colleagues [22] found the MAC of the S(+) isomer to be 1.44% *vs* 1.69% for the R(–) isomer (racemate 1.59%). Although the S(+) isomer was found to be the more potent, this difference was not statistically significant. Overall, these findings suggest that any enantiomer-selective effect for volatile anaesthetics may be relatively weak. However, the evidence is much stronger for specific drug–receptor interactions when the modes of action of intravenous agents are considered (Table 1).

Intravenous anaesthetics

Thiopental, methohexital, ketamine and etomidate are all chiral compounds. While the first three are used as racemates, etomidate is given as the single R(+) isomer. Propofol is not a chiral compound.

S(+)-thiopental has a shorter terminal half-life than the R(+) isomer [13] because of its more rapid metabolism and clearance. These differences extend to the metabolite, pentabarbital. There have been few studies comparing the effects of separate administration of the two thiopental isomers, although in the early 1970s this was performed in the mouse model [33] and the S-enantiomer was found to be more potent. This was confirmed by Mark and colleagues[58] in a study in human volunteers.

More recent animal work[59] has confirmed that S-thiopental is more potent when assessed by depression of EEG activity, but is associated with a lower therapeutic ratio. In one study, three out of seven animals died in the S-thiopental group and recovery from EEG depression was slower. An earlier study[60] using a similar experimental model confirmed this better therapeutic ratio for the R enantiomer and suggested that it may be due to a greater distribution in CNS tissue than heart.

In vitro studies of possible CNS receptor target sites have been performed in order to explain the greater potency of the S-isomers. Minimal stereoselectivity was at α-amino-3-hydroxy-5-methylisoxazolepropionic acid (AMPA) receptor[44] and nicotinyl acetylcholine receptor[18] sites, making it unlikely that they are pivotal in producing barbiturate anaesthesia. Study of expressed human $GABA_A$ receptors[15] produced differences in median effective concentration (EC_{50}) for S-thiopental [26 (SD 3.2) μM], rac-thiopental [35.9 (4.2) μM] and R-thiopental [52.5 (5) μM], and these values are consistent with the differences in potency for CNS depressant effects found *in vivo.*

Methohexital, although no longer used in the UK, is of interest as it contains two asymmetrical centres, one at position 5 in the barbiturate ring and the other the initial carbon on the 1-methyl-2-pentynyl side-chain. This produces two pairs of stereoisomers.[13] One pair are enantiomers and the other pair are diastereomers (i.e. they are not mirror images). It was used clinically as a mixture of the two least excitatory isomers. Methohexital and thiopental also exhibit tautomerism (dynamic isomerism). In alkaline solution, sodium thiopental is highly water-soluble because of an ionized side-chain. When injected into plasma at pH 7.4, this becomes a non-ionized, non-dissociated form which rapidly isomerizes to its tautomer, a highly lipid-soluble compound.

Steroid anaesthetic agents, while not currently used in clinical practice, also exhibit chirality. Pregnanolone and allopregnan-3-ol-20-one both contain eight chiral centres (C-3, C-5, C-8, C-9, C-10, C-13, C-14 and C-17), which leads to complex stereochemistry. A recent study looked at two enantiomers of each compound.[16] Stereoselectivity was evaluated both *in vivo* (GABA receptor effects in rat brain membrane preparations) and *in vitro* (loss of righting reflex in tadpoles and mice). The results showed that 5α-reduced steroids, but not 5β-reduced steroids, show a high degree of enantioselectivity/enantiospecificity in their actions as modulators of $GABA_A$ receptors and as anaesthetics. For all compounds studied, the effects on $GABA_A$ receptor function closely tracked the anaesthetic effects. These data show that the anaesthetic steroid recognition site is capable of distinguishing enantiomers, suggesting a protein-binding site of specific dimensions and shape.

Etomidate is used as a single isomer in clinical practice. The anaesthetic effect resides predominantly in the R(+) enantiomer, which is approximately five times as potent as the S-isomers.

Tomlin and colleagues[76] studied the EC_{50} required to induce loss of the righting reflex in tadpoles. R(+)-etomidate had an EC_{50} of 3.4 (SD 0.1) μM compared with 57 (1) μM for S(+)-etomidate. They also studied the isomeric effects on GABA-induced currents in mouse fibroblasts that had been stably transfected with bovine $GABA_A$ receptors, using a patch-clamp technique. The R(+) isomer was much more effective in potentiating GABA-induced currents, although the degree of stereoselectivity varied with anaesthetic concentration. The two isomers were equally effective in disrupting lipid bilayers. These findings are consistent with the theory that the effects on the $GABA_A$ receptor are central to the anaesthetic activity of etomidate.

Lambert's group[9] further examined the nature of the interaction between etomidate and the mammalian $GABA_A$ receptor. They used the *Xenopus laevis* oocyte expression system in conjunction with two-point voltage clamping to assess the effects of a single-point amino acid substitution in one of the GABA receptor subunits on the response to R(+)-etomidate. They found that a single-point mutation on the β_3 subunit completely abolished the allosteric regulation of the $GABA_A$ receptor by etomidate. This finding is further evidence for the specificity of anaesthetic action.

Harrison and colleagues have also investigated site-directed mutagenesis. In separate studies, specific mutations at serine 270 in the $GABA_A$ receptor α subunit were found to alter the sensitivity of the receptor to enflurane and isoflurane.[51 62] Harrison's recent editorial also expands on the theory of anaesthetic-binding pockets or cavities within target molecules such as the NMDA or the GABA receptor, and how specific mutations may affect areas which border the anaesthetic binding domains.[36 37]

Ketamine, a phencyclidine derivative, produces dissociative anaesthesia rather than the generalized CNS depression seen with other intravenous induction agents. It is also unique in that it has significant analgesic effects and does not depress the cardiovascular system. However, ketamine's adverse effect profile, such as emergence delirium and excessive cardiovascular stimulation, has meant that its use has been limited in general anaesthetic practice.

In vitro studies using guinea-pig brain homogenate have examined the binding affinity the chiral forms of ketamine with phencyclidine and opioid receptors.[41] Binding affinity was highest for the phencyclidine receptor and exhibited stereospecificity with a S(+)/R(–) ratio of 2.5 in favour of the S(+) isomer. The high binding affinity accords with the theory that the anaesthetic and analgesic effects of ketamine result from NMDA receptor blockade. Binding affinity for the κ opioid receptor was 20–30 times lower but still exhibited stereospecificity [S(+)/R(–) ratio 4.2]. Affinity for the μ opioid receptor was lower still and had an S(+)/R(–) ratio of 2.5. Enantiomer-specific effects have also been demonstrated for human sodium channels,[28] while studies of muscarinic receptors have produced conflicting results.[29 73]

Pharmacological data reveal that the metabolism of S(+)-ketamine by human liver microsomes[47] is 20% greater than that of the R(–) enantiomer and 10% greater than that of the racemate, giving a faster clearance of drug. The production of similar pharmacodynamic effects with a smaller dose of drug and faster clearance gives S(+)-ketamine an attractive pharmacological profile for further investigation.

In human volunteers, Adams and colleagues[1] compared intravenous rac-ketamine 2 mg kg^{-1} with S-ketamine 1 mg kg^{-1}. They found equivalent cardiovascular stimulation but more rapid recovery in the S-ketamine group. Doenicke and colleagues[17] compared equivalent doses of rac- and S-ketamine but added a third group, who were premedicated with intravenous midazolam. The expected increase in mean arterial pressure (MAP) was identical in the first two groups but abolished in the midazolam group. Recovery of visual attentiveness and sensorimotor performance was better in the S-enantiomer group, as was subjective assessment of mood. Midazolam prevented any unpleasant emergence sequelae at the expense of slower recovery of cognitive performance.

When comparing subanaesthetic doses, Pfenninger and colleagues[68] found equivalent analgesic effect and cardiovascular stimulation but less anterograde amnesia and better recovery of concentration with S-ketamine.

Clinical studies have also been performed examining the use of ketamine in coronary artery bypass surgery[83] and orthopaedic surgery.[10] The cardiac study compared rac- and S-ketamine at three time points: at induction, during steady-state fentanyl–midazolam anaesthesia, and at aortic cross-clamping during extracorporeal circulation. At each point, a bolus of racemate 3 mg kg^{-1} or S-enantiomer 1.5 mg kg^{-1} was given. Monitoring included invasive arterial blood pressure, right heart pressure and volume, left ventricular systolic and end-diastolic pressures, and maximum speed of left ventricular pressure increase. During intubation, heart rate and MAP increased to a similar degree in the two groups. Overall, there was no major difference in the haemodynamic profiles of rac- and S-ketamine.

During orthopaedic (knee) surgery, anaesthesia was induced with midazolam and either rac-ketamine 2 mg kg^{-1} or S-ketamine 1 mg kg^{-1}. A continuous infusion of racemate 1 mg^{-1} kg^{-1} h or S-enantiomer 0.5 mg^{-1} kg^{-1} h was then given throughout surgery in addition to vecuronium and N_2O/O_2. The authors found no difference in cardiovascular variables. Clinically, therefore, the cardiovascular effects of the S-enantiomer are indistinguishable from those of the racemate.

Analgesics
The use of S-ketamine may have greater potential as an analgesic than as a general anaesthetic. At low rates of infusion, the cardiovascular side-effects are not seen and the advantages of avoiding opiate-induced side-effects are apparent. It can also be administered via a variety of different routes. S-ketamine, when given by caudal block in paediatric anaesthesia,[57] provides postoperative analgesia equivalent to that of bupivacaine. Its use in adult acute pain services could also be expanded. Arendt-Nielsen and colleagues[5] found that the S-isomers reduced temporal and spatial summation of pain in a post-burn model in human volunteers and also had the advantage of producing less slowing of reaction time than the racemate.

Tramadol
Tramadol hydrochloride is a chiral analgesic with a novel, dual mode of action. It has weak affinity for the μ opioid receptor (10 times less than codeine)[69] but, more importantly, increases central neuronal synaptic levels of 5-hydroxytryptamine and norepinephrine. These neurotransmitters are involved in antinociceptive descending pathways in the spinal cord. Tramadol has two chiral centres, in positions 1 and 2 in the cyclohexanol ring, giving rise to four stereoisomers.[13] Clinically, it is used as a mixture of two enantiomers, (1R, 2R)(+)-tramadol and (1S, 2S)(–)-tramadol.

The effects of the stereoisomers have been looked at in animal models. The actions of rac-, (+)- and (–)-tramadol on electrically evoked norepinephrine efflux and uptake, measured by fast cyclic voltammetry, were studied in the rat locus coeruleus brain slice.[79] Rac-tramadol and its enantiomers all significantly increased the stimulated level of norepinephrine efflux. However, only (–)-tramadol blocked norepinephrine reuptake, increasing the reuptake half-time to 499 (SD 63)% of the predrug value. These findings are in agreement with those of other studies.[19 74]

Stereoselectivity is also found with the effects on the serotonergic system. Raffa and colleagues[70] found the (+) enantiomer to be the most potent inhibitor of serotonin uptake in the mouse model. In addition, they found that both enantiomers produced an antinociceptive effect in the acetylcholine-induced abdominal constriction test. Rac-tramadol was significantly more potent than the theoretical additive effect of the enantiomers. Their finding of antinociceptive synergy in the rat Randall–Selitto yeast-induced inflammatory nociception model was also demonstrated in the mouse 55°C hotplate test.

These experimental findings indicated that, interestingly, the racemate would be the optimum formulation for clinical use. Grond and colleagues[32] confirmed this clinically by looking at the use of tramadol in patient-controlled analgesia after major gynaecological surgery. Patients were given an individualized loading dose of up to 200 mg and were randomized to (+)-, (–)- or rac-tramadol PCA with an on-demand dose of 20 mg. The primary endpoint was a decrease in pain score. Failure to reach this endpoint was most frequent in the (–) enantiomer group [53% *vs* 12% in the (+)-tramadol and 15% in the rac-tramadol group]. Of the patients who reached the primary endpoint, more were in the (+) enantiomer group [67% *vs* 48% in the rac-tramadol and 38% in the (–)-tramadol group]. The percentage of patients satisfied with their pain relief in the first 24 h after surgery was 82, 76 and 41% for the (+)-, (rac)- and (–)-tramadol groups respectively. Nausea and vomiting was the most common side-effect and was seen most frequently in the (+)-tramadol group. It was concluded that the racemate was superior to the enantiomers when efficacy and side-effects were considered together.

Dexmedetomidine
Medetomidine, an imidazoline compound, is a very potent, selective and specifically full agonist at both pre- and postsynaptic α_2-adrenoceptors.[82] It is used widely in veterinary anaesthesia. Its inhibition of sympathetic tone in the CNS leads to a characteristic pattern of pharmacodynamic responses, including hypotension, bradycardia, sedation, anxiolysis, analgesia and hypothermia. These effects can be inhibited or reversed by administration of the selective and specific α_2-antagonist atipamezole.[82] This finding forms a strong basis for the use of atipamezole as a reversal agent against medetomidine-induced effects in veterinary practice (e.g. at the end of surgical procedures).

In receptor binding experiments, the α_2/α_1 selectivity ratio of medetomidine is 1620 compared with 220 and 160 for clonidine and xylazine respectively. The α_2-adrenoceptor activity of medetomidine resides almost solely in its D-enantiomer, i.e. dexmedetomidine.[82]

In the rat brain,[55] dexmedetomidine causes sedation and hypothermia and induces a dose-dependent decrease in the release and turnover of norepinephrine, dopamine and 5-hydroxytryptamine, features characteristic of α_2-agonists. It has an MAC-sparing effect when given to beagles[81] anaesthetized with halothane and also decreases heart rate and cardiac output.

Volunteer studies have confirmed this MAC-sparing effect with isoflurane. Ebert's group[21] examined the cardiovascular, respiratory and endocrine effects of increasing doses of dexmedetomidine infusions. Monitoring included direct arterial, central venous and pulmonary artery pressures, cardiac output, oxygen saturation, end-tidal carbon dioxide, arterial blood gas analysis and catecholamine concentrations. The catecholamine concentrations were significantly reduced at the initial dose level and the increase in norepinephrine seen during the cold pressor test was abolished. There was a dose-dependent increase in sedation and reductions in heart rate, mean arterial pressure, pulmonary artery pressure, cardiac output and stroke volume. Recall and recognition were reduced at a dose greater than 0.7 ng ml^{-1}. Respiratory variables were minimally affected and acid–base status was unchanged.

The effects of dexmedetomidine have been studied both during and after surgery. Aho and colleagues,[2] in a double-blind, randomized, controlled trial with 20 patients undergoing hysterectomy, compared dexmedetomidine infusion with placebo. The infusion was commenced 10 min before induction of anaesthesia and was then set at a maintenance rate that was given throughout. Isoflurane was administered according to predetermined criteria. In the dexmedetomidine group, the isoflurane requirement was reduced by >90%.

In another study of 41 patients undergoing major vascular surgery,[75] an infusion of dexmedetomidine or saline was started 20 min before induction of anaesthesia and continued until 48 h after surgery. Heart rate stability was greater in the dexmedetomidine group, and this group also had a significantly smaller increase in norepinephrine concentrations in the immediate postoperative period.

When dexmedetomidine or placebo was used for sedation and analgesia in 119 patients requiring ventilation after cardiac or general surgery,[80] the dexmedetomidine group required significantly less midazolam or morphine.

Further investigation of this compound will help define its role in intensive care and also in relation to anaesthesia[66] and acute pain.

Dextromethorphan

Dextromethorphan is the dextrorotatory isomer of the codeine analogue levorphanol. It is widely used for its central antitussive action and has weak affinity (10-fold less than codeine) for the μ opioid receptor.[69] In the normal dose range it has no analgesic or sedative effects and it is not a respiratory depressant. In addition, it is a non-competitive antagonist at the NMDA receptor. This property has led to its experimental use in a number of clinical areas, such as acute and chronic pain and neuroprotection after brain injury.

In acute pain studies, antagonism of the NMDA receptor should theoretically reduce central hypersensitization (wind-up) and so reduce analgesic consumption and/or pain scores. Dextromethorphan has been given before[30 38] and after[39] surgery and has had modest effects on both analgesic consumption and pain scoring. In chronic pain, it has been used alone and in combination with morphine (Morphidex).[45] There is evidence to suggest not only that it augments the analgesic effect of opioids but also that it blocks or reduces the development of tolerance after long-term opioid administration.[23]

NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) originate from a structurally diverse group of compounds and inhibit the synthesis of prostaglandin at one or more steps in the endoperoxide biosynthetic pathway. Some of the groups from which they arise are chiral and these include the largest group, the 2-arylpropionic acids (2-APAs) or 'profens'. Additionally, other arylalkanoic acids (e.g. ketorolac, etodolac) and some miscellaneous compounds (e.g. azapropazone) are also chiral.

It has been recognized for a number of years that the major or exclusive *in vitro* inhibition of prostaglandin synthesis is elicited by the S enantiomer.[24] This has resulted in the introduction into clinical practice of a number of single-isomer NSAIDs, including S-naproxen, S-ibuprofen and, more recently, S-ketoprofen. These drugs aim to achieve a faster onset of action, enhanced potency and the promise of diminished side-effects. From a theoretical standpoint, advantages exist in marketing single-isomer NSAIDs as the dose selection is simplified, pharmacokinetic profiles are less complex and drug interactions less likely to occur. This in turn enables more rational prescribing and better understanding of nociceptive and inflammatory processes. However, further evaluation is needed before an appropriate assessment of their comparative safety can be realized.

Neuromuscular blocking drugs

Pancuronium, vecuronium and rocuronium are all aminosteroid derivatives and, like other steroid molecules, contain multiple asymmetrical centres. However, the manufacturing process is such that a single stereoisomer is produced and used clinically.[13]

Atracurium and mivacurium possess four chiral centres and so theoretically they may exist as one of 16 possible stereoisomers.[13] Atracurium is synthesized in a non-selective manner but internal symmetry reduces the number of stereoisomers to 10. Each can be classified by its configuration at the two carbon atoms (R or S) and by its relative configuration at the two carbon–nitrogen bonds (*cis* or *trans*). The isomers can be divided into three groups of geometrical isomers: *cis–cis, trans–trans* and *cis–trans*. There are considerable differences in their pharmacokinetics and pharmacodynamics. The 1R-*cis*,1R-*cis* isomer (cisatracurium) is the most active and potent. Although the neuromuscular blockade it produces is similar to that given by atracurium, atracurium produces little or no histamine release and significantly lower laudanosine concentrations.[7] Mivacurium consists of three geometrical isomers. The predominant (94%) *cis–trans* and *trans–trans* isomers are equipotent, have a high clearance rate (4.74 litre h^{-1} kg^{-1}) and very short elimination half lives (approximately 2 min).[7] In contrast, the *cis–cis* isomer has a lower clearance rate, longer half-life and much lower potency.

Local anaesthetics

In 1969, Luduena first demonstrated that the enantiomers of 2′,6′-pipecoloxylide derivatives show significant differences in local anaesthetic action.[52] The S(−) enantiomers of both mepivacaine and bupivacaine were found to be longer-lasting, mirroring earlier experiments on the enantiomers of prilocaine. This early work also found that

S(−) bupivacaine was considerably less toxic than the R(+) isomer (both intravenously and subcutaneously) in small animal species, yet without any apparent loss of potency.

While interesting, these results were not relevant, given that the large-scale commercial synthesis of enantiomerically pure local anaesthetics was not feasible. In addition, the release of bupivacaine as a racemate had heralded many advantages over its predecessors. Its prolonged duration of action reduces the need for repeated administration, sensory block is more prominent than motor block (the so-called sensorimotor split) and the drug is highly potent. This last characteristic is also its Achilles heel, however, as highlighted by Albright's editorial in 1979.[3] Sudden cardiovascular collapse, occasionally with no premonitory symptoms, prompted a re-evaluation of the potential advantages to be gained by reformulating the drug as a single-isomer preparation, i.e. levobupivacaine. Commensurate with this has been the release of ropivacaine, the S(−) enantiomer of propivacaine. Both have been the subject of recent reviews[54 56] and, despite ongoing debate concerning their relative potencies, are long-acting agents with a wide spectrum of action. In addition, the evidence to suggest that they have a more benign side-effect profile is considerable.

Levobupivacaine has been shown consistently to be less toxic than rac-bupivacaine (bupivacaine) in all animal studies. It is less arrhythmogenic and shows a trend towards more effective resuscitation and has a higher convulsive threshold, and the lethal dose range is of about 1.3- to 1.6-fold higher.[14 40]

A study by Bardsley and colleagues[8] in human volunteers, using thoracic bioimpedence to evaluate cardiac contractility, compared the effects of intravenous levobupivacaine and bupivacaine. An infusion of each drug was administered at the rate of 10 mg min^{-1} until CNS symptoms appeared or 150 mg had been given. Despite a higher mean plasma concentration of levobupivacaine than bupivacaine (2.38 *vs* 1.87 µg ml^{-1}), levobupivacaine had less effect on the mean stroke index [−5.2 (SD 7.4) *vs* −11.9 (8.4) ml m^{-2}, P =0.001], the acceleration index [−0.09 (0.15) *vs* −0.2 (0.16) s, P=0.001] and the ejection fraction [−2.5 (3.3) *vs* −4.3 (3.9)%, P=0.02]. Another study in human volunteers examined the electroencephalographic (EEG) effects after an intravenous dose of levobupivacaine 40 mg, bupivacaine 40 mg or placebo.[72] Both drugs produced a characteristic slowing of the EEG, consistent with CNS depression, but levobupivacaine had effects that were less both in magnitude and in the amount of the brain involved.

A similar method was used in an earlier comparison of the effects on the CNS and cardiovascular system of an intravenous infusion of ropivacaine, bupivacaine and placebo in 12 healthy volunteers.[48] Objective CNS signs (e.g. muscular twitching, dysarthria) or symptoms were observed in 10 subjects in the ropivacaine group as opposed to all the subjects receiving bupivacaine. The mean time from cessation of the infusion to their disappearance was shorter in those receiving ropivacaine [13 (SD 11) *vs* 20 (16) min, P<0.05], despite a higher tolerated dose and a concomitant higher free plasma concentration (0.56 *vs* 0.30 mg litre^{-1}, P<0.001). At doses producing CNS symptoms, cardiovascular changes (depression of conduction, diastolic function) were less pronounced with ropivacaine than with bupivacaine.

The available animal data therefore point in the same direction: the single-isomer drugs are less toxic. The available human data, although for lower doses, follow this trend and it therefore seems logical to assume that the single-isomer drugs are safer in man. Supportive evidence is provided by recent case reports describing accidental intravenous administration of both drugs.[49 50] However, only their widespread introduction into clinical practice will allow us to truly ascertain their value.

Summary

The chirality that is inherent in the enzyme systems of living organisms results in an abundance of enantiopure organic molecules in the living world. In addition to the optical properties first noticed by Pasteur, stereospecific interactions at recognition sites result in differences in both biological and toxicological effects. This fact underlies the continuing growth in chiral chemistry, rooted as it is in fundamental biochemistry.

The pharmaceutical industry has undergone a strategic shift and embraced the wide spectrum of asymmetrical synthetic methods now available. The use of these processes in developmental synthesis and large-scale manufacturing has provided new challenges in drug discovery, motivated by a desire to improve industrial efficacy and decrease the time from the conception of a new drug to the market. The economic impact of the industrial production of chiral drugs is now huge—more than 50% of the 500 top-selling drugs were single-enantiomers in 1997. Sales have continued to increase by more than 20% for the past 6 yr and worldwide annual sales of enantiomeric drugs exceeded US$100 billion for the first time in the year 2000, chiral drugs representing close to one-third of all sales worldwide.

While some 'chiral switches' may be of less apparent benefit, or indeed detrimental in some cases, encouragement by the regulatory agencies and the ability to extend the life cycle of a drug coming off patent promotes the trend. However, it may turn out to be the ability to provide chiral templates, and thereby attack the key targets of selectivity and specificity, that will lead to the greatest benefits. Research into new chemical entities that can interact specifically with enzyme families may potentially lead to new therapies for complex disease processes. As Richards[71] has stated, the approach is designed to create a *made to measure product*, rather than one *off the peg*.

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BJA

SHORT COMMUNICATIONS

The postanaesthesia care unit as a temporary admission location due to intensive care and ward overflow†‡

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Background. With the increasing number of critically ill patients, and shortage of intensive care unit and ward beds, some postoperative patients stay for an unnecessarily long period in the postanaesthesia care unit (PACU), until a suitable bed is available.

Methods. We prospectively studied this patient overflow admission to the PACU over 33 months. Four hundred patients with a mean age of 53.1 yr (range 0.2–94) were studied. Two hundred and eighty one (70.3%) patients were mechanically ventilated on admission to the PACU and 311 (77.8%) had invasive monitoring. Mean length of stay in the PACU was 12.9 (SD 10.6) h.

Results. The busiest hours of admission were 01–11 am. Eighteen (4.5%) patients died in the PACU, while waiting for an intensive care unit bed. The main problems were insufficient medical and nursing coverage, and inadequate communication and visiting facilities for patient's families.

Conclusion. Patient overflow to the PACU is a common problem that requires attention. Guidelines for medical and nursing coverage, patient triage, and communication with relatives need to be outlined.

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For several years, there has been an increased demand to treat critically ill patients in the intensive care unit (ICU). Yet, due to budget constraints, the number of ICU beds is limited. To the same extent, several hospital wards are fully occupied, due to a discrepancy between the number of patients and the number of available beds. We have recently admitted several patients into the postanaesthesia care unit (PACU), because they did not have a bed available in one of the hospital's ICUs or wards. A study was therefore conducted to quantitate the number of these patients and evaluate the various problems associated with this practice.

Methods and Results

The study database included: patients who remained in the PACU after surgery due to the lack of an available bed in an ICU or in the regular ward; patients who were triaged to the PACU from the emergency room for weaning from mechanical ventilation (usually trauma patients with negative radiology studies); patients who needed preoperative preparation for emergency surgery; and patients who remained in the PACU for extended observation. Extended observation was indicated by the attending anaesthetist and surgeon for patients who were in a stable postoperative condition, but because of their general medical status, or the extent of surgery, it seemed prudent to monitor them overnight in the PACU. An intermediate (high dependency) care area is not available in our hospital. We excluded all patients who had a bed available in their postoperative destination location, and patients who had only a short period (up to a few hours) of postoperative mechanical ventilation.

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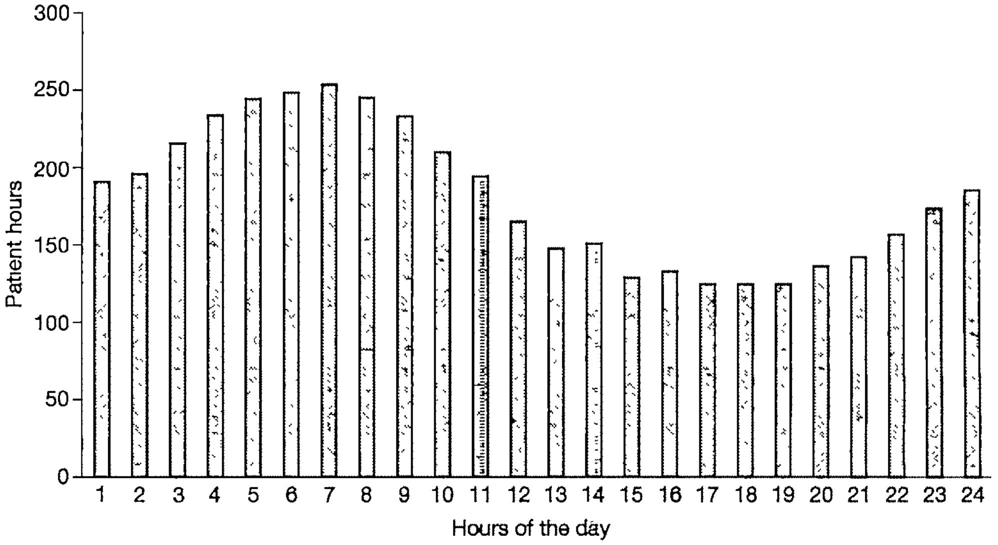

Fig 1 Total number of patient-hours in the postanaesthesia care unit at any hour of the day during the study period

Table 1 Patient assignment before PACU admission, and actual discharge destination. ICU, intensive care unit; PACU, postanaesthesia care unit *0 as only available in PACU †Died before discharge

Location	Assignment before PACU admission	Actual discharge destination
	n (%)	*n* (%)
Medical/surgical ICU	177 (44.3)	109 (27.2)
Neurosurgical ICU	84 (21.0)	60 (15)
Neurosurgical ward	39 (9.8)	45 (11.3)
Other wards	22 (5.5)	136 (34.0)
Other ICUs	20 (5.0)	13 (3.2)
Extended observation	37 (9.2)	0*
To surgery	0	18 (4.5)†
Died in PACU	0	18 (4.5)
Other	21 (5.2)	1 (0.3)
Total	400 (100)	400 (100)

Our 10 bed PACU is staffed 24 h a day, 7 days a week. The nurse to patient ratio varies over 24 h from 1:1 to 1:4, depending on nurse staffing and patient load. A resident or a staff anaesthetist, who is covering both the operating room and the PACU, is available at any time.

The data were collected from April 1998 to December 2000. During the study period, 23 787 patients were admitted to our PACU, of whom 400 (1.7%) were recorded in the study database. There were 250 (62.5%) males and 150 (37.5%) females, with a mean age of 53.1 years (range 0.2–94, median 58 yr). Seventeen patients (4.2%) were under the age of 10 years. Two hundred and thirty-one patients (57.8%) were admitted directly from the emergency room, either after surgery or to the PACU without needing surgery. The most common surgical procedures were: neurosurgery (108 patients (27.0%)); abdominal surgery (79 (19.8%)); and trauma/orthopaedic surgery (61 (15.2%)). Fifty (12.5%) patients had no surgery before or after PACU admission. On admission to the PACU, 281 patients (70.3%) were mechanically ventilated and 311 (77.8%) had invasive monitoring. The mean length of stay in the PACU was 12.9 (SD 10.6) h (range 0.5–68, median 10.8 h). Forty-one patients (10.3%) stayed in the PACU longer than 24 h. Figure 1 shows the number of hours all the patients had been in the PACU (patient-hours) at any hour of the day. The busiest hours were 01–11 am, suggesting that many patients were admitted to the PACU during the night, and were discharged the next day.

In respect of patient load related to nursing shifts, 38.8% of patient-hours were on the night shift, 36.7% on the morning shift and 24.5% on the evening shift. One hundred and seventy-one (42.8%) patients were admitted to the PACU during the night shift, 71 (17.7%) during the morning shift, and 158 (39.5%) patients during the evening shift.

Lack of available bed for discharge was the most common reason for PACU stay (342 patients, 85.5%). The planned patient assignment before PACU admission, and actual discharge destination are listed in Table 1. Two hundred and eighty-one patients (70.3%) were assigned to one of the seven medical, surgical or paediatric ICUs, which have a total of 70 beds One hundred and nineteen (29.7%) patients were assigned to a regular hospital ward. One hundred and eighty-two patients (45.5%) were discharged to one of the hospital ICUs, and 181 (45.3%) were discharged to a regular ward. The main administrative problems included missing radiology files, missing surgical reports, and missing parts of the patient's chart. Patients' triage to an ICU, or a busy ward was more difficult during the evening and night shifts.

Comment

The PACU is primarily established to minimize the incidence of complications immediately after anaesthesia and surgery, while providing the best quality of safe care. Our study demonstrates that the PACU at a busy major (900 bed) general hospital may function clinically as an ICU or as a temporary admission ward. The excellent nursing and anaesthesia coverage, the monitoring capabilities and the potential space, makes the PACU an attractive location to admit these patients. However, PACUs were neither designed, staffed nor equipped to serve as an ICU. The greatest patient load and number of admissions occurred in the night shift, the time of minimal nursing and medical coverage. At this time of day, iatrogenic incidents are more common.[1,2] The American Society of Post Anesthesia Nursing recommends that two licensed nurses should be present in the PACU, even when only one patient is being recovered.[3] In our experience, during the night shift, one PACU nurse cared for all the study patients, in addition to caring for 'routine' post-emergency surgery recovery patients. Medical coverage was also a common problem. The surgical team responsible was often unavailable for advice, or for medical/surgical follow-up of their patients. In many cases, the PACU patients were excluded from the surgical rounds. An updated electronic medical record may provide a solution to some of the various administrative problems.

The issue of PACU admission due to bed overflow is poorly reported in the medical literature. A nursing journal recently published two manuscripts on this topic.[4,5] Physician coverage was the most challenging issue described in these reports. Other problems included: nurse staffing; patient safety and privacy; and documentation.[4,5] Patients' families were also a major concern in our study. The operating theatre is a protected area where a minimum number of people are expected to visit. On most occasions, patients met their family only after discharge to the ward. However, for critically ill and trauma patients who stay for a longer period of time in the PACU, we cannot ignore the family need to visit. This might become a major problem when the patient is not expected to survive beyond a few hours. At times, several family members insist on visiting their critically ill relative. In addition, the PACU is not the appropriate location to handle the process of organ donation. This situation of dying patients and bereaved families has a direct negative influence on other PACU patients and their families.

How do we deal with these problems? Appropriate allocation should be assigned to every patient on admission to hospital. The staff of the ICU, or the ward to which the patient is assigned, should make every effort to find an appropriate bed. This may necessitate moving other patients who are recovering, either within the same ward or ICU or to another location. Since our PACU is staffed 24 h a day, there is no need to use the expensive ICU for basic or even complex postoperative patient care.[6] But if patient overflow occurs, the PACU undertakes the role of the ICU.[7] A designated PACU space with appropriately trained nurse staffing and medical care should therefore be provided. The nurse staffing should be flexible, since patient overflow may occur at any time during the day or night. Social and other family services should be available. Guidelines should be outlined for family visiting and for communication with the physicians responsible for the patient. The PACU should be an integral part of the surgical round, and surgical consultation should be available any time. An anaesthetist should be available to care solely for PACU patients

Patient overflow to the PACU is an institutional challenge. It can be managed successfully by a multidisciplinary approach.

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Radial artery cannulation: topical amethocaine gel *versus* lidocaine infiltration

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Background. In a prospective randomized study, we compared topical 4% amethocaine gel (Ametop^{TM}) with 2% lidocaine infiltration for analgesia for radial artery cannulation. A previous study had shown topical analgesia with EMLA cream reduced pain, shortened cannulation time, and improved success rates when compared with lidocaine infiltration.

Methods. One hundred adult patients undergoing elective cardiac surgery were randomized. Cannulation times and success rates were compared between the two groups. The quality of analgesia was assessed using a visual analogue scale (VAS) and four-point verbal pain scoring system.

Results. Ninety-nine sets of data were analysed using Mann–Whitney *U* and chi-squared tests. Mean time to cannulation was 56 s in the amethocaine group (interquartile range (IQR) 41–142) and 59 s in the lidocaine group (IQR 40–105). The median pain score on the VAS was 2 in both groups (IQR 1–3.5 for amethocaine and 0–4 for lidocaine).

Conclusions. There was no significant difference between these two methods of analgesia for any measured variable.

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Radial artery cannulation is a painful procedure, and standard analgesia is subcutaneous infiltration with lidocaine before cannulation. Topical analgesia with EMLA cream has been shown to shorten cannulation time, improve the success rate, and reduce the pain of radial artery cannulation.[1] Despite these findings, EMLA cream is not widely used for this procedure, and this may be because of the slow onset of action of EMLA (2 h). Compared with EMLA, 4% amethocaine provides a faster onset and longer duration of analgesia for venous cannulation.[2] We postulated that the vasodilatory properties of amethocaine might further improve the speed and success rate of radial artery cannulation by arterial dilatation and prevention of reflex vasoconstriction. In this study, we evaluated the use of topical 4% amethocaine gel for arterial cannulation by comparing it with lidocaine infiltration.

Methods and results

We recruited 100 adult patients undergoing elective cardiac surgery. The study received ethical approval and informed consent was obtained from all patients. Patients with an abnormal Allen's test or known sensitivity to local anaesthetics were excluded from the study. Patients were randomized to receive either topical 4% amethocaine gel (Ametop™) or 2% lidocaine infiltration. Amethocaine gel was applied to both wrists under an occlusive dressing over the proposed puncture site at least 1 h before attempted arterial cannulation. Alternatively, 2% lidocaine (0.5–0.7 ml) was infiltrated with a 25-gauge needle at least 1 min before attempted arterial cannulation. All patients received premedication with lorazepam 1–3 mg, 2 h before transfer to the anaesthetic room.

Before arterial cannulation, the wrist was hyperextended over a gauze roll. The occlusive dressing and excess amethocaine gel were removed, or 2% lidocaine infiltrated, according to randomization. An experienced registrar or consultant anaesthetist attempted cannulation with a 20-gauge Abbocath™ cannula (Baxter).

Immediately after the procedure, each patient was asked to complete a 10 cm visual analogue scale (VAS): 0=no pain, 10=worst pain imaginable; and a verbal pain score

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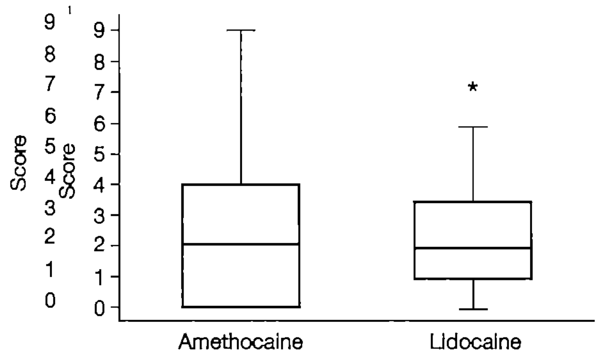

Fig 1 Box and whisker plot for VAS pain scores (median, IQR) No significant difference shown

(VPS): 0=no pain, 1=mild, 2=moderate, 3=severe pain. These pain scales were discussed with the patient at the preoperative visit.

We measured the time to successful cannulation. The clock started as the cannula touched the skin to start cannulation and stopped as soon as the arterial line was connected. Failure to cannulate within 10 min or procedures abandoned earlier were classed as failures. Additional lidocaine was infiltrated in patients who complained of pain or looked uncomfortable.

This requirement for additional lidocaine was noted, in addition to any erythema of the amethocaine gel site.

One-tailed power analysis suggested that the study had 80% power to detect a difference in cannulation time of 45 s between the groups (SD 90 s). Power analysis was one tailed, as we were primarily interested in a result in favour of amethocaine. The SD of 90 s used in power analysis was an estimate based on a small pilot study assuming normal distribution. However, the study data were not normally distributed and further statistical analysis used Mann–Whitney *U* and chi-squared tests. The statistical analysis was performed with SPSS v. 9.0 on a Windows based PC.

Of 100 patients enrolled, one was too sedated to give a pain score and his data were excluded; this left 99 sets of data for analysis. Both groups were similar in terms of age, sex, height, weight, and operative procedure (P=0.55–0.85). Median time to cannulation was 65 s for the amethocaine group, IQR 41–142, and 59 s for lidocaine, IQR 40–105 (95% confidence intervals for difference −13.99 and 29.02, respectively). Four-point pain scoring by the patient showed a median of 2 in both groups (IQR 1–3.5 for lidocaine and 0–4 for amethocaine, P=0.93, 95% confidence intervals were −1.0 to 1.0).

The median, IQR, and range of VAS for pain are shown in Figure 1. Failure to cannulate occurred in five of the amethocaine group and seven of the lidocaine group (P=0.54); this failed cannulation rate of 12% correlates well with rates reported previously.[3,4] Additional lidocaine was required in seven of the lidocaine group and 11 of the amethocaine group (P=0.54). There was no correlation between the failure to cannulate and additional lidocaine. There were no serious skin reactions to the amethocaine application. Erythema of the proposed cannulation site was common.

Comment

A number of studies have shown EMLA to be superior to lidocaine infiltration in providing analgesia for radial artery cannulation.[1,5–7] A study by Joly and colleagues compared EMLA and lidocaine infiltration in over 500 patients and found superior analgesia, a higher success rate and shorter cannulation times in the EMLA group.[1] Against this background, our results appear surprising until the studies are compared more closely. We cannulated the radial artery with a 20-gauge cannula whereas the study by Joly and colleagues used an 18-gauge cannula and a 5f sheath. The latter allocated unpremedicated patients according to day of surgery: that is all patients on 1 day received topical infiltration and those on the next day, EMLA. Patients in our study were premedicated. Although premedication with a benzodiazepine does not provide analgesia, it is well recognized that a premedicated patient may perceive and recall pain differently. The populations were slightly different, in that Joly's patients were attending for coronary angiography, and ours for cardiac surgery. These two groups may perceive the importance of good analgesia for arterial cannulation differently.

It is also worth noting that our sample size is smaller than Joly's study. Based on our power analysis, 100 patients were required to detect a mean difference in time to successful arterial cannulation of 45 s. We feel that this is the minimum mean difference required to justify the greater effort and expense in the use of amethocaine gel in clinical practice. Presently, one tube of Ametop™ gel costs £1.15 and a 5 ml ampoule of 2% lidocaine costs 23 pence.

We have shown that in premedicated patients, topical 4% amethocaine gel and lidocaine infiltration are equally effective in providing analgesia for radial artery cannulation. Success rate and speed of cannulation were also similar for both methods. As amethocaine gel is both more expensive and time consuming to apply, we cannot recommend its routine use for arterial cannulation instead of lidocaine infiltration.

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Postoperative sore throat after ambulatory surgery

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Background. Sore throat is a common complication of anaesthesia that affects patient satisfaction after surgery.

Methods. We studied 5264 ambulatory surgical patients prospectively to determine the patient, anaesthetic, and surgical factors associated with sore throat.

Results. In 5264 patients, 12.1% reported a sore throat. Patients with tracheal tube had the greatest incidence, 45.4%, followed by patients with laryngeal mask airway, 17.5%, while patients with a facemask had a lower incidence of sore throat, 3.3%. Female patients had more sore throats than male patients (13.4 vs 9.1%). Airway management had the strongest influence on the incidence of sore throat. Sore throat in ambulatory surgical patients was associated with female sex, younger patients, use of succinylcholine, and gynaecological surgery.

Conclusion. Airway management, female sex, younger patients, surgery for gynaecological procedure, and succinylcholine predicts postoperative sore throat. Increased awareness of the predictive factors can help to avoid this combination and improve patient satisfaction.

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Keywords: complications, sore throat; surgery, ambulatory

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Sore throat is a common complication after surgery. It affects patient satisfaction and can affect the patient's activities after leaving hospital.[1–3]

Several factors contribute to postoperative sore throat. Reporting of a sore throat can be affected by whether this symptom is asked about directly or indirectly.[4] The incidence varies with the method of airway management. Tracheal intubation (ETT) is associated with a greater incidence of sore throat than laryngeal mask airway (LMA[†]) or facemask (FM).[2] Studies of postoperative sore throat have not distinguished ambulatory surgical patients from inpatients. We set out to determine which patient characteristics and operative factors predict sore throat in ambulatory surgical patients.

Methods and results

We enrolled 17 638 consecutive ambulatory surgical patients in a prospective observational study over 3 yr with ASA physical status I, II, and III, aged 12 yr and older. The hospital's ethics committee approved the study.

We recorded the patients' age, sex, weight, height, and ASA physical status on a standardized information sheet. The type and duration of surgery, operative airway management (ETT, LMA, or FM) tracheal tube size, patient position during surgery, drugs given, and duration of stay in

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[†] LMA® is the property of Intavent Limited.

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Table 1 Multiple logistic regression—stepwise backward elimination. Predictors of sore throat

	OR	95% CI	*P* value
Age, 10-yr increments	0.92	0.85–0.98	<0.05
Sex, male/female	0.76	0.59–0.99	<0.05
ASA III *vs* I/II	0.45	0.21–0.94	<0.05
Postoperative stay, increments of 30 min	1.05	1.01–1.10	<0.05
Suxamethonium	1.67	1.25–2.23	0.0005
ETT *vs* FM	12.40	8.83–17.39	0.0001
LMA *vs* FM	5.26	3.79–7.29	0.0001
Ophthalmology	0.58	0.40–0.84	0.01
Gynaecology	1.52	1.14–2.03	0.01

the postanaesthetic care unit and ambulatory surgical unit (ASU) were also recorded.

An aqueous lubricant was applied to the tracheal tube and LMA airway cuffs. A standard method was used for placement of tracheal tubes and LMA. After ETT, patients lungs were mechanically ventilated, and patients with LMA breathed spontaneously. After intubation or placement of an LMA, anaesthesia was maintained with an inhalation agent in a mixture of oxygen and nitrous oxide. Patients with an FM received oxygen only. Airway devices were removed when patients were able to open their eyes to command.

The clinical management of the patients was left to the discretion of the anaesthetist. Postanesthesia Discharge Score (PADS) was used to decide when to discharge the patient.[5] All patients were discharged on the same day as the surgery. An ASU nurse interviewed the patient by telephone after 24 h and the incidence of sore throat was noted by using standardized direct questions. Patients were asked directly whether they had a sore throat, and whether they had any hoarseness of voice.

Statistical analysis

The incidence of sore throat was compared between different patient groups using chi-squared statistics. Continuous variables were compared between patients with and without sore throat using Student's *t*-test. We used multiple logistic regression modelling with backward stepwise variable selection to identify factors associated with sore throat. Variables with $P>0.1$ were eliminated from the model. Statistical analysis was with SAS statistical software, version 6.12 (SAS Institute Inc., Cary, NC, USA).

During the study period, 17 877 patients were to undergo ambulatory surgery. A total of 239 patients were excluded as a result of cancellation or incomplete data. Of the remaining 17 638 patients, a successful telephone interview was conducted with 5264 patients (29.84%). Of the non-respondents, 5878 (33.3%) refused to give an interview, 2169 (12.3%) did not speak English, and 4327 (23.6%) could not be contacted. There was no significant difference between respondent and non-respondent in mean age or duration of anaesthesia. The response rate was greater for patients after procedures for urology (38%), general surgery (37%), ENT or dental surgery (33%), orthopaedic surgery (32%), or ophthalmology (31%): patients after gynaecological procedures were less likely to give an interview (27%).

The mean age was 47 yr (range 16–85). Two-thirds of the patients were female, one-third of the patients were male. Most of the patients had procedures for ophthalmological, gynaecological, or orthopaedic conditions (38, 31, and 19%, respectively). A tracheal tube was used in 14.3% of patients, an LMA in 19.4% of patients, an FM in 62.8%, and no airway management was used in 3.5% of the patients.

Of the 5264 patients, 12.1% (635) reported a sore throat. Patients with ETT had the greatest incidence (45.5%, 345 of 755), followed by patients with LMA (17.5%, 178 of 1020), whereas patients with FM had a lower incidence of sore throat (3.3%, 108 of 3303). In the patients with sore throat, the duration of stay in PACU was 14 min longer ($P<0.05$), the duration of ASU stay 25 min longer ($P<0.05$), and discharge time 51 min longer ($P<0.05$).

Univariate analysis showed that female patients had more sore throats than males (overall 13.4 *vs* 9.1%, ETT 50.1 *vs* 32.5%, LMA 21.6 *vs* 13.6%, and FM 3.9 *vs* 1.7%; $P<0.05$ for all comparisons).

After surgery in the lithotomy position, patients had more sore throat compared with patients after surgery in the supine position (ETT 56.0 *vs* 35.7%, LMA 25.0 *vs* 16.1%, and FM 5.9 *vs* 1.9%; $P<0.05$ for all comparisons). Patients given succinylcholine also had more sore throat than patients not given this agent (51.3 *vs* 35.8%; $P<0.05$). Ease of intubation was not associated with the development of postoperative sore throat (46.4%) compared with 47.8% in patients with difficult intubation.

After gynaecological surgery, patients had a greater risk of sore throat compared with other patients (ETT 57.4 *vs* 31.6%, LMA 25.3 *vs* 16.5%, FM 5.9 *vs* 2.0%; $P<0.05$ for all comparisons). In patients managed with an LMA, orthopaedic patients had less sore throat than other patients (15.1 *vs* 23.2%, $P<0.05$), and in patients managed with an FM, patients after ophthalmic procedures had less than other patients (1.7 *vs* 5.3%, $P<0.05$). Univariate analyses showed no other statistically significant associations.

Multiple logistic regression

A multiple logistic regression model with stepwise variable selection was set up including all subjects. Variables included in the model at the first step of variable selection were: age, sex, ASA status, BMI, duration of surgery, duration of postoperative stay, position of patient, succinylcholine use, type of airway management, and type of surgery. Table 1 shows the variables that remained in the final model.

Men had less chance of sore throat than women (odds ratio (OR) 0.76). Age was inversely associated with the risk of sore throat (OR for a 10-yr increment 0.92). Patients with ASA physical status III had a significantly smaller risk of developing sore throat compared with patients with ASA physical status I and II (OR 0.45). The duration of postoperative stay was positively associated with the risk of sore throat development (OR for a 30-min increment 1.05). The use of succinylcholine was also a strong predictor for postoperative sore throat (OR 1.67). The method of airway management had the strongest influence on the risk of sore throat. A sore throat was 12 times more common in patients with ETT, and five times more likely with LMA than in patients with FM or no airway management. Two types of surgical procedures were significantly different from the others. Patients undergoing ophthalmic procedures had a significantly smaller risk (OR 0.58), whereas patients undergoing gynaecological procedures had a significantly greater risk (OR 1.52) of developing sore throat, as compared with other types of surgical procedures.

Comment

A previous study of 381 ambulatory surgical patients found postoperative sore throat in 22% of patients after ETT and 9% of patients managed with a LMA.[6] We found a greater incidence of 45.5 and 17.5%, respectively. There are several possible factors: we did not use humidity moisture exchangers in the gas delivery circuit, and dry airway gases have been implicated in the development of postoperative sore throat.[7] Airway suction is associated with postoperative sore throat, and this was not standardized. Tracheal and LMA were placed by both residents and staff, with a wide range of experience. Greater operator skill improves ease of placement.[8] The pressures in tracheal and LMA cuffs were not monitored during surgery and cuff volumes were not adjusted. Decreasing LMA cuff volume during surgery reduces the incidence of postoperative sore throat.[9] In conclusion, postoperative sore throat is a common adverse outcome in ambulatory patients. The method used for airway management has the strongest influence on the incidence of sore throat. Female sex, younger patients, surgery for gynaecological procedures, and succinylcholine also predict postoperative sore throat. The association between postoperative stay and sore throat could result from the discomfort of a sore throat early in the postoperative period making patients reluctant to go home. By knowing these patient characteristics and operative factors, awareness of the problem is increased and can help to avoid this combination, and improve patient satisfaction.

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ProSeal laryngeal mask protects against aspiration of fluid in the pharynx[†]

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Background. The ProSeal laryngeal mask airway (PLMA) is a new device designed to isolate the airway from the digestive tract.

Methods. We studied the ability of the PLMA to isolate the airway in 103 anaesthetized adults who were breathing spontaneously or given neuromuscular blocking agents, by filling the hypo-

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pharynx with methylene blue-dyed saline introduced down the drainage tube once the mask was in place. At the beginning and end of the procedure, a fibre-optic bronchoscope was passed down the airway tube to observe any dyed saline in the bowl of the mask.

Results. The PLMA was positioned correctly in all successful attempts (102 out of 103 attempts) and was able to isolate the glottis from fluid in the hypopharynx in all patients initially. Leakage of saline into the bowl of the mask occurred in two patients in whom displacement of the mask was caused by upper airway events during the procedure. In the remaining 100 patients, the glottis was isolated successfully for the duration of the procedure.

Conclusions. The PLMA can be positioned reliably. It can isolate the airway from fluid in the hypopharynx.

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Keywords: equipment, masks anaesthesia; larynx, bronchoscopy fibreoptic; complications, aspiration; complications, regurgitation

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The ProSeal laryngeal mask airway (PLMA, Intavent Orthofix, Maidenhead, UK) is a new device with features designed to isolate the airway from the digestive tract and prevent fluid aspiration.[1] We investigated the ability of the PLMA to isolate the airway in anaesthetized adults. The hypopharynx was filled with methylene blue-dyed saline introduced down the drainage tube after the mask had been placed. At the beginning and end of the procedure, a fibre-optic bronchoscope was passed down the airway tube to detect any leakage of dyed saline into the bowl of the mask.

Methods and results

One hundred and three adult patients were studied as part of a larger study.[2] Ethics committee approval was obtained from the research ethics committee of the Faculty of Medicine of the University of Cape Town, and all patients gave informed written consent. We studied patients undergoing elective surgery in which a classic laryngeal mask airway would normally be used. Patients were excluded if they were at risk of aspiration. Anaesthesia was induced with fentanyl 1 μg kg^{-1} followed 2 min later by propofol 2–3 mg kg^{-1} until loss of eyelash reflex. In spontaneously breathing patients, the PLMA was inserted immediately after induction, when adequate jaw relaxation had been achieved. Patients to be ventilated were given a non-depolarizing neuromuscular blocking agent chosen at the discretion of the investigator at a dose appropriate for tracheal intubation. The PLMA was inserted 2–3 min later. Anaesthesia was maintained by isoflurane with nitrous oxide 66% in oxygen using a circle absorber system. A PLMA size 4 in females and size 5 in males was inserted using either the index finger or the introducer tool. The cuff was inflated to obtain an intracuff pressure of 60 cm H_2O as measured by a calibrated aneroid manometer. The intracuff pressure was maintained at this pressure throughout the procedure by adjusting the air in the cuff if the intracuff pressure changed.

A fibre-optic bronchoscope (Olympus BF 240) was introduced down the airway to a position 1 cm proximal to the end of the tube. If the view showed that the mask was rotated or distorted without surrounding the glottis, the test was halted and the reason noted. Normal saline dyed with methylene blue was prepared by adding methylene blue 20 mg to normal saline 1 litre. The dyed saline was previously found to be easily visible through the bronchoscope when present within the bowl of the PLMA. The dyed saline was introduced down the drainage tube until the hypopharynx was filled and a column of saline flowed back up the drainage tube to form a meniscus outside the patient's mouth at the level of the lips. *In vitro* testing found that the volume of methylene blue required to fill the drainage tube until the meniscus reached the level corresponding to the patient's lips was 7 ml in a size 4 PLMA and 10 ml in a size 5 PLMA; the height of this column was found to be 12 cm above the tip of the mask. The presence or absence of a leak into the bowl of the mask was noted via the bronchoscope. If a leak was present, the process was halted, the saline suctioned from the tube and the case noted as a failure. The fluid in the hypopharynx and column of blue saline was then left in the drainage tube for the duration of the procedure, the meniscus being maintained by adding further amounts of methylene blue saline if necessary. The total amount of methylene blue saline used was recorded. In the event of any change in respiratory measurements combined with a drop

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Table 1 Details of anaesthesia

	Number of patients
Neuromuscular blockade	
Yes	66
No	37
Position of patient	
Supine	55
Lithotomy	26
Trendelenburg	15
Sitting	2
Lateral	4

in the level of the meniscus, airway endoscopy was repeated to see if a leak had occurred within the mask. If so, the saline was suctioned out and a failure noted. Otherwise, at the end of the procedure the bronchoscope was reintroduced and the bowl of the mask reinspected for any signs of leaked blue saline. The bronchoscope was then removed and the saline aspirated from the drainage tube.

The details of anaesthesia are shown in Table 1. Placement of the PLMA was unsuccessful in one patient.

Endoscopic airway inspection revealed no cases of mask malposition. Consequently, dyed saline was introduced down the drainage tube in all patients. The total volume of methylene blue-dyed saline introduced down the drainage tube during the procedure was 16.9 (6–30) ml for a size 4 and 28.4 (12–60) ml for a size 5. In every case, endoscopic inspection revealed an uninterrupted column of dyed saline within the distal portion of the drainage tube visible within the bowl of the mask. The oesophagus was not visible within the bowl of the mask in any cases. No incidences of leakage of saline into the bowl of the mask or oropharynx occurred on initial introduction of the saline down the drainage tube. No leakage of saline into the bowl of the mask or oropharynx occurred at any time in 100 patients (98%). Saline leaked into the bowl of the mask during the procedure in two patients (2%). One leak occurred in a 46-yr-old man undergoing an incision and drainage of a tibial abscess. A size 5 PLMA had been inserted easily on the first attempt and inflated with 35 ml of air. Gastric tube placement had been achieved easily. Total volume of dyed saline introduced down the drainage tube during the procedure was 35 ml. He had received fentanyl 1 μg kg^{-1} for analgesia and was breathing spontaneously when he coughed in response to surgical incision 7 min after induction of anaesthesia. On reintroduction of the bronchoscope, the mask was found to be displaced to the right with a small amount of dyed saline in the bowl of the mask. The saline was suctioned out and the anaesthetic continued uneventfully. Another leak occurred in a 72-yr-old male with chronic obstructive airway disease undergoing optical urethrotomy. A size 5 PLMA had been placed easily on the first attempt and inflated with 38 ml of air. Gastric tube placement had been achieved easily and the total volume of dyed saline introduced was 38 ml. He had received fentanyl 1 μg kg^{-1} for analgesia and was breathing spontaneously when he developed laryngospasm during the urethrotomy 20 min after induction. Dyed saline was seen leaking out of the mouth and on reintroduction of the scope the bowl of the mask was filled with dyed saline. The saline was suctioned out and anaesthesia deepened, but subsequently proceeded uneventfully.

Comment

The PLMA was positioned correctly in all successful placements and at first isolated the glottis from fluid in the hypopharynx in all patients. A leak into the bowl of the mask occurred later in two of 102 patients during the procedure. In the remaining 100 patients the glottis was isolated successfully for the duration of the procedure.

In all but one case, the volume of dyed saline injected into the drainage tube was greater than the volume of the tube, indicating that the saline must have entered the hypopharynx. We presume that in the one case in which a smaller volume was injected an airlock must have occurred within the tube.

This study has shown that the properly positioned PLMA can isolate the airway from fluid contained within the hypopharynx in paralysed and non-paralysed patients, even when that fluid is present for a considerable period of time and the patient is in a variety of positions, including head-down. This study did not mimic the act of passive regurgitation, as the fluid did not travel up the oesophagus. However, the pressure attained in the drainage tube, and therefore, presumably, within the hypopharynx during this study (12 cm H_2O) is greater than that normally associated with passive regurgitation, but less than the described maximum pressures of 30 cm H_2O.[3] The study by Brimacombe and colleagues in cadavers[4] showed that, when the drainage tube was closed, the PLMA successfully protected the airway from fluid injected up the oesophagus until pressures of 63–68 cm H_2O had been achieved. If the drainage tube was left open, no leaks occurred.

It is therefore reasonable to conclude that the PLMA is likely to provide better protection of the airway from passive regurgitation than either no airway protection device or the classic laryngeal mask airway.

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No evidence of mutations in the *CACNA1S* gene in the UK malignant hyperthermia population†

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Background. Malignant hyperthermia (MH) is an inherited, potentially fatal, pharmocogenetic disorder triggered by certain anaesthetic agents. In light of the reported genetic heterogeneity for the disorder and the recent introduction of DNA testing guidelines for the trait, we have assessed the role of the *CACNA1S* gene in MH susceptibility in UK patients. Linkage to this locus has previously been demonstrated in several European MH families.

Methods and results. We screened 200 unrelated MH-susceptible individuals for known *CACNA1S* mutations. With the aim to characterize further novel mutations at this locus, functionally relevant regions of the gene were also sequenced in 10 unrelated individuals from families where the involvement of other MH susceptibility loci was unlikely. No sequence variations were detected in any of the patients investigated.

Conclusions. Defects in *CACNA1S* are not a major cause of MH in the UK population. Diagnostic screening of this gene is unlikely to be of value to UK MH patients in the near future.

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Malignant hyperthermia (MH) is an autosomal dominant inherited disorder in which a serious disturbance in skeletal muscle calcium regulation occurs when an individual is exposed to previously demonstrated potent inhalational anaesthetics or depolarizing neuromuscular blocking drugs. Without rapid intervention, a patient suffering an MH crisis may die. For the last 30 years, the only reliable method to determine an individual's MH status has been by the *in vitro* contracture (IVC) test, whereby a muscle sample is biopsied and subsequently exposed to incremental doses of either caffeine or halothane and the relative contracture responses determined.[1] In 2001, the European MH group published guidelines for the introduction of genetic testing for the condition.[2]

Genetic analyses mapped the MH susceptibility trait to the ryanodine receptor locus (*RYR1*) on chromosome 19q12–13.2. This gene encodes the skeletal muscle sarcoplasmic reticulum calcium release channel, a key protein involved in the process of excitation–contraction coupling. To date, over 30 different mutations have been detected in the gene,[3] and 15 of these have been functionally characterized using *in vitro* cellular assays and are considered causative of MH.[2 4] It is important to demonstrate that these mutations have a 'pathogenic' effect in a functional assay, as the majority of mutations identified in MH patients are missense mutations (amino acid substitutions), which may have a minimal effect on normal calcium channel function. Approximately 25% of UK MH pedigrees

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Table 1 Primer sequences used for *CACNA1S* sequence analysis

CACNA1S exon	Primer sequence 5′–3′	
	Forward	**Reverse**
14	CTC CCT TCC ACC TAC AAC CA	GGC ATC ACG ACT GAG CAC T
15	TGG GAT CCT CTG AAG GTG TT	AGG TGC TCA CCT TGG CAG T
16	AAC GCT AAC AGG CTC TCC AG	CCC TAC TTC ACC CCA GCA C
17	AGC AAA GCA TGG GAA GAC AC	AGA TGA GAG CCG CAT CAA TC
18	CTC CAG CAG CTC ACA GCT C	CTG GGC ACC AGA CTG AGG
25	CCA CCC AGT CTG TCC TCT CT	CTC TGC CCT TCC ACC TCT G
26	TCT TGG TGC TGA CCT GTC CT	ATC CTG CCC TAC TCA TCC TG

carry one of the 15 causative MH mutations. Whilst other, currently undetected, mutations in *RYR1* may be responsible for a large percentage of MH cases (up to 50% show linkage), exclusion of linkage between MH susceptibility and *RYR1* has been reported on numerous occasions.[5] Linkage studies have implicated other candidate loci on chromosomes 1q, 3q, 5p, 7q and 17q. Therefore MH can be said to be a condition showing considerable allelic and locus heterogeneity.

Monnier and colleagues[6] determined linkage to the *CACNA1S* gene on chromosome 1q with a high degree of probability (two-point LOD score of +4.38) in a large French MH pedigree. *CACNA1S* encodes the α1 subunit of the dihydropyridine receptor (DHPR), a transverse tubule calcium channel that is tightly coupled to the ryanodine receptor.[7] The DHPR functions as the voltage sensor in excitation–contraction coupling. Upon further sequence analysis of MH-susceptible individuals within the pedigree, a G-to-A change at nucleotide 3333 in exon 25 of the *CACNA1S* gene, substituting arginine for histidine at amino acid 1086, was discovered, which segregated completely with the MH phenotype. This represented the first direct molecular evidence of MH locus heterogeneity. Subsequently Jurkatt-Rott and colleagues[8] have found a similar amino acid substitution (Arg1086Cys) in exon 25 that displays partial segregation with the MH phenotype in a German pedigree. Both exons 25 and 26 of *CACNA1S* encode the intracellular loop that links domains III and IV within the DHPR α1 subunit. Although the functional significance of this region remains unclear, one model suggests that it in some way participates in signalling with the ryanodine receptor.

The aim of this study was to determine whether mutations in the *CACNA1S* gene predispose the UK population to MH susceptibility. Results of such analyses could have implications for the genetic diagnosis of MH in the future.

Methods and results

A cohort of 200 unrelated IVC-tested MH-susceptible individuals representative of the UK MH population was tested to determine the presence or absence of the G3333A mutation (exon 25 of DHPR α1s) using a restriction enzyme digest assay.[6] This sample size was sufficient to detect a mutation with <1% prevalence. Final analysis provided us with no evidence of this mutation existing within the UK MH population, giving an estimated frequency of <0.25% (upper 95% confidence interval: 0.75%) in this group. We concluded that alongside further investigation of this domain (III–IV linking region), other regions of the DHPR α1s that interact with the ryanodine receptor protein should be analysed for possible MH associated mutations. The II–III cytoplasmic loop, an important determinant in excitation–contraction coupling,[9] is one such region encoded by the *CACNA1S* exons 14 to 18.[10]

A group of MH-susceptible individuals representing 10 UK MH pedigrees was selected. Three exhibited discordance between the *RYR1* genotype and MH-susceptibility phenotype, implying the possible presence of a second/alternative causative mutation, or linkage to another susceptibility locus. One represented a pedigree in which a known *RYR1* mutation (G7300A) completely segregated with the MH phenotype and therefore served as a *CACNA1S* mutation negative control. The remaining seven represented pedigrees in which known mutations were excluded and evidence of linkage to chromosome 19 was inconclusive. Genomic DNA samples from all representative MH-susceptible individuals were amplified by the polymerase chain reaction using exon-specific primers for exons 14–18 and 25–26 (Table 1) and sequenced.

No sequence variations were identified within this cohort for the regions investigated. Therefore mutations in *CACNA1S*, or at least these specific regions, do not appear to be a significant cause of MH in the UK MH population. It would also suggest that exons 14–18 and 25–26 are highly conserved regions of the gene and are therefore crucial to the normal function of the DHPR.

Comment

As our investigation has provided no evidence of mutations in the *CACNA1S* gene in the UK MH population, there is currently no basis to propose adding mutation screening of *CACNA1S* to that of *RYR1* in guidelines for the DNA-based diagnosis of MH for UK patients.[2] Screening for mutations in this gene may, however, be beneficial in the assessment of

MH status in other populations. Further studies examining physical or functional interactions between the DHPR and the ryanodine receptor may highlight other regions in the α1 subunit that may harbour mutations causative of MH. Alternatively, other genes of the DHPR heterotetramer complex – β and γ subunit genes on chromosome 17q, and the α2/δ subunit gene on chromosome 7q – may warrant investigation. Numerous potential candidate genes have been proposed for MH on the basis that they code for proteins involved in skeletal muscle calcium homeostasis, the disruption of which appears to be the primary physiological defect in patients suffering an MH reaction. Examples include genes coding for triadin, calsequestrin and the tacrolimus-binding protein, FKBP12. Genetic analysis to date would indicate that, if involved, such candidates are likely to be rare susceptibility loci. Evidence indicates that defects in the *RYR1* gene account for the majority of MH cases. Future research may therefore be better prioritized towards determining the presence of novel mutations within this locus.

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CASE REPORTS

Transoesophageal echocardiographic monitoring of pulmonary venous obstruction induced by sternotomy closure during infant heart transplantation

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A case of an infant receiving orthotopic heart transplantation with over-sized donor heart was reported. Left lower pulmonary venous obstruction after sternotomy closure was detected by transoesophageal echocardiography (TOE) and the decision to delay sternal closure was made and the clinical outcome was very satisfactory. The usefulness of intraoperative TOE monitoring and postoperative TOE follow-up for infant heart transplantation, especially in those cases of size mismatch, was well demonstrated.

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Keywords: heart, orthotopic heart transplantation; complications, pulmonary venous obstruction; monitoring, transoesophageal echocardiography

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Intraoperative transoesophageal echocardiography (TOE) is a useful tool for the immediate evaluation of pulmonary venous anastomoses and allows immediate surgical correction during lung transplantation.[1–4] We would like to report a case of an infant receiving orthotopic heart transplantation, in whom left lower pulmonary venous obstruction after sternotomy closure was detected by TOE and the decision to delay sternotomy closure was made. The sternotomy was closed safely on the fourth postoperative day. The usefulness of TOE during size mismatch infant heart transplantation is well demonstrated.

Case report

A 6-month-old, 4 kg boy with hypertrophic cardiomyopathy had been diagnosed immediately after birth with left ventricular outflow tract obstruction and right ventricular outflow tract obstruction complicated by refractory congestive heart failure. Despite medical control, his condition deteriorated and he was put on the waiting list for heart transplantation at 3 months of age.

This patient received standard orthotopic heart transplantation with a donor heart from a 13-month-old, 11 kg girl who had died as the result of an astrocytoma of the brain. Anaesthesia was induced with i.v. ketamine 2 mg kg^{-1}, and maintained with fentanyl 10 μg kg^{-1} h^{-1} infusion. Pancuronium was used for neuromuscular block. CVP and arterial pressure monitors were placed smoothly after induction of anaesthesia.

TOE was performed by a cardiac anaesthesiologist trained in the use of TOE. A specially designed TOE probe for newborns and infants (GE Vingmed Ultrasound) was used. This probe is 6.5 mm in external diameter and 50 cm in length, with a 7.5 MHz, monoplane and colour flow Doppler transducer. For insertion of the TOE probe the patient was placed supine with his head in the midline position. The transducer tip covered with sterile Surgilube was introduced gently into the oesophagus. Before surgery, the TOE image showed all four chambers to be severely dilated with poor contractility. After skin incision, a short run of ventricular tachycardia with hypotension was controlled with medication and the patient was put on cardiopulmonary bypass immediately. The recipient's heart was removed by transecting the atrio-ventricular grooves, posterior to both atrial appendages. The aorta and pulmonary artery were transected at the level of the

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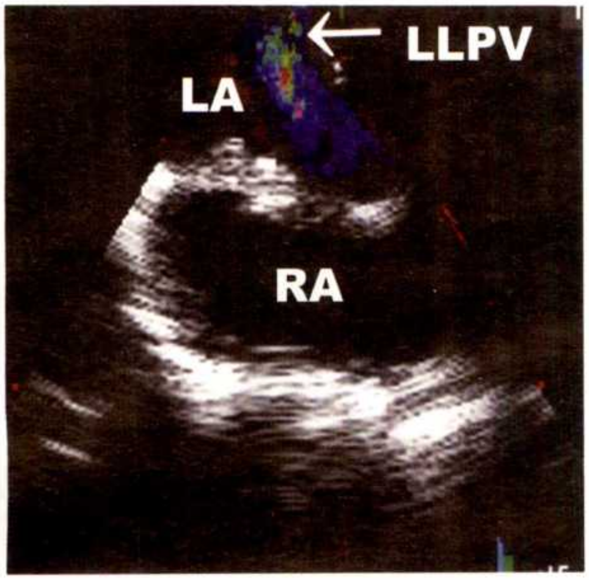

Fig 1 After cardiac transplantation from an 11 kg donor, left lower pulmonary venous obstruction was detected by mosaic pattern (arrow) of colour flow Doppler image of TOE.

commissures of the semilunar valves. Implantation of the donor heart was started by anastomosis of the left atrium with a continuous suture, followed by anastomosis of the right atrium and pulmonary arteries. The aortic anastomosis was carried out last. The total ischaemic time was 180 min.

After weaning from cardiopulmonary bypass, infusion of nitroglycerin (0.5 $\mu g\ kg^{-1}\ min^{-1}$) and dopamine (8 $\mu g\ kg^{-1}\ min^{-1}$) were started. TOE showed no obvious regional wall motion abnormality, valvular stenosis, or regurgitation. Unfortunately, when the surgeon approximated the sternotomy, the patient's oxygen saturation (Sp_{O_2}) fell gradually from 99 to 92–95%. The problem was not resolved by careful suction of the trachea or adjustment of the ventilator settings. No significant fall in arterial pressure was noted. Left lower pulmonary venous obstruction was detected as a mosaic pattern of colour flow Doppler image on TOE with a peak flow velocity of 1.5 $m\ s^{-1}$ (Fig. 1). The surgeon opened the sternotomy to check the anastomoses and no obvious anatomic problem was found. The TOE showed that the peak flow velocity of the left lower pulmonary vein had decreased to 1.0 $m\ s^{-1}$. The patient's Sp_{O_2} increased gradually back to 99%. We concluded that pulmonary venous obstruction was a result of an oversized donor heart being placed in the relatively small pericardial cavity. We decided to keep the sternotomy open, separating the sternal edges with a 1 cc syringe and the wound was covered with a surgical membrane.

After transfer to the surgical intensive care unit, the patient's condition stabilized and inotropic agents were tapered gradually. After discontinuing the infusions, hypertension was controlled with propranolol and captopril. A TOE examination on the fourth postoperative day showed no more pulmonary venous obstruction and the sternotomy was closed. The patient made an uneventful recovery and was discharged on the 28th postoperative day.

Discussion

Orthotopic heart transplantation is a widely accepted therapeutic measure for adult patients with end-stage heart disease. Although cardiac transplantation is currently an accepted treatment for infants and children with end-stage heart failure, and inoperable complex congenital defects,[5 6] it is under-used in newborns and infants because of a shortage of donor organs. Most authors consider that large donor-sized size mismatches can be well tolerated in infant and paediatric heart transplantation.[7] Some authors even believe that the use of an oversized donor heart might be beneficial, particularly in those with pre-transplantation pulmonary hypertension. However, a high incidence of transient lobar or complete lung collapse in transplants with a high donor-to-recipient weight ratio has been reported.[7] Tweddell and colleagues predicted the need for prolonged ventilator support when a donor-to-recipient weight ratio is greater than 2.[8] On the contrary, use of undersized donor hearts is associated with poor results and should be strongly discouraged.[9]

In our case with a donor-to-recipient ratio of 2.75, problems of donor–recipient size mismatch were anticipated. Under TOE monitoring, we found marked left lower pulmonary venous obstruction detected as a mosaic flow pattern of the colour flow Doppler image. This finding changed the surgical management. The delay of sternal closure relieved the pulmonary venous obstruction and may have contributed to the prevention of lung complications such as lobar collapse or lung congestion. After several days of donor heart remodelling,[10 11] the sternotomy was closed successfully and bedside TOE confirmed that pulmonary venous obstruction did not recur.

A possible alternative cause of the pulmonary venous obstruction was compression of the left atrium by the TOE probe placed in the oesophagus, we think this unlikely because of the clear association between the obstruction and sternal closure.

In summary, we report a case of an infant receiving orthotopic heart transplantation, in whom left lower pulmonary venous obstruction after sternotomy closure was detected by TOE and the decision to delay sternal closure was made with a good clinical outcome. The usefulness of intraoperative TOE monitoring and postoperative TOE follow-up for infant heart transplantation, especially in those cases of size mismatch, was well demonstrated.

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Oesophagotracheal perforation after intraoperative transoesphageal echocardiography in cardiac surgery

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Although transoesophageal echocardiography (TOE) can be considered a safe procedure, severe complications may occur. We report an oesophagotracheal perforation diagnosed 7 days after a complex and very long four-valve replacement procedure in a patient with a poor preoperative condition. We believe that an ischaemic lesion of the oesophagotracheal wall caused by the TOE probe was the initial event leading to this perforation. This observation raises concerns about the safety of prolonged TOE monitoring and suggests that a combination of risk factors (i.e. a small stature, a very long procedure, congestive heart failure, and a low cardiac output before and after cardiopulmonary bypass) may warrant increased precautions while performing TOE during cardiac surgery.

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Transoesophageal echocardiography (TOE) is routinely performed in the operating room in cardiac surgery. It is generally considered a semi-invasive technique with a very low rate of complications. We report here a fatal case of oesophagotracheal perforation diagnosed after intraoperative TOE monitoring in a 37-yr-old patient undergoing elective four-valve replacement at our institution.

Case report

The patient, a 37-yr-old man, weight 47 kg, height 1.70 m, was to undergo bioprosthetic valve replacement of the aortic, mitral, tricuspid, and pulmonary valves. Eight years earlier he had had a trivalvular bioprosthetic replacement (aortic, mitral, and tricuspid valves) with a

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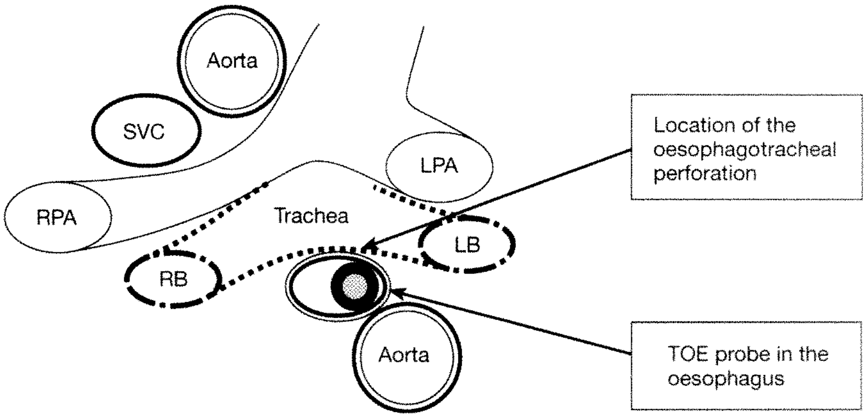
Aorta
SVC
RPA
Trachea
LPA
RB
LB
Aorta
Location of the oesophagotracheal perforation
TOE probe in the oesophagus

Fig 1 Schematic drawing of an anatomic section of the upper mediastinum illustrating the relationship between the oesophagus (with the TOE probe) and the tracheal bifurcation and showing the location of the oesophagotracheal perforation in our patient. (Abbreviations: SVC, superior vena cava; RPA, right pulmonary artery; LPA, left pulmonary artery; RB, right bronchia; LB, left bronchia.)

pulmonary valve repair for complex congenital and rheumatic heart disease.

Several weeks before the re-operation he presented with right ventricular (RV) failure. Degeneration of all three bioprosthesis and severe pulmonary regurgitation was diagnosed using transthoracic echocardiography. The left ventricle was enlarged with a moderate reduction in left ventricular ejection fraction. The right ventricle was enlarged and hypertrophic. The pulmonary systolic pressure was 65 mm Hg. Preoperative oesophagogastroscopy was normal.

During surgery the patient was monitored with a radial artery catheter, a Swan-Ganz pulmonary artery catheter with Sv_{O_2}, and TOE. The ultrasound transducer (Multiplan V5M, Acuson, Mountain View, CA) was inserted without difficulty at the first attempt. A small nasogastric tube was inserted easily at the end of the surgical procedure.

The surgical procedure was complex and long, lasting 9 h including a total cardiopulmonary bypass (CPB) duration of 6 h at a mean arterial pressure of 50–70 mm Hg. The TOE probe remained in the oesophagus during the whole procedure. The tip of the probe was in the neutral position, at the level of the left atrium in the oesophagus, and the transducer was disconnected during bypass. CPB was uneventful.

Weaning from CPB was difficult because of a low cardiac output and pulmonary hypertension, which required an infusion of epinephrine and dobutamine and the insertion of an intra-aortic balloon pump (IABP). During the early postoperative period the patient remained unstable with bleeding and low cardiac output with RV failure. The mean arterial pressure was around 60–70 mm Hg for 36 h despite inotropic and vasoconstrictive pharmacological support. After 3 days of intensive care, IABP was removed and inotropic drugs were gradually withdrawn. The patient's condition gradually improved but on postoperative day 7 he presented with clinical signs of shock and epinephrine had to be resumed. Bilateral pulmonary infiltrates appeared on the chest x-ray and the patient became severely hypoxaemic. A gas leak became obvious during ventilator insufflations despite correct positioning of the orotracheal tube and an intact balloon cuff. During a fibre optic bronchoscopy (performed for broncho-alveolar lavage before antibiotic treatment) we found a 5-mm round hole surrounded by a pale ring of false membrane located at the posterior, membranous face of the tracheal bifurcation, just above the left main bronchus and we diagnosed an oesophago-tracheal perforation. Oesophageal mucous membrane was clearly seen through the hole. The rest of the tracheal and bronchial mucous membrane was normal. Broncho-alveolar lavage culture subsequently revealed a streptococcal pulmonary infection and one blood sample on the same day was positive for the same bacteria. A Blackemore oesophageal balloon catheter was inserted. Surgical repair was planned but the patient died a few hours later. An oesophagoscopy was not performed. The patient's family refused an autopsy.

Discussion

TOE is used routinely in cardiology, cardiac surgery, and ICU for diagnostic or monitoring procedures. It is generally considered a safe and minimally invasive technique. However, adverse events may occur during insertion or manipulation of the probe. Serious complications are reported in less than 0.1% of TOE examinations with a mortality rate around 0.004% without definitive evidence of a direct link.[1] TOE may be associated with gastrointestinal trauma, dysphagia, laceration, perforation, or haemorrhage.[2–6] As far as we know, this is the first report of an oesophagotracheal perforation complicating this procedure.

Bleeding and perforations are mostly traumatic, occurring during probe insertion and are rapidly recognized during the early post-procedure period, leading to prompt surgical treatment. In our case, the complication became obvious only on the seventh postoperative day leading to a fatal bilateral pneumonia. Recently, Massey and colleagues reported the case of a fatal oesophageal perforation recognized on the fourth postoperative day, highlighting the difficulty of an early diagnosis of such a complication in intensive care patients.[7] The principal risk factor for this perforation was gross cardiomegaly which displaced and thinned the patient's oesophagus. As in our observation the delayed expression and recognition of the perforation contributed to the fatal outcomes.[7]

In our case, the location of the perforation and its timing strongly support the hypothesis that the underlying pathophysiological mechanism was ischaemia of the oesophageal and tracheal mucous membranes caused by contact pressure between the echo probe and the tracheobronchial wall in a region of intimate proximity of the oesophagus and the tracheal bifurcation (Fig. 1). As documented by the preoperative endoscopy, the lesion occurred in a macroscopically normal oesophagus. The pressure caused by TOE probes was studied by Urbanowicz and colleagues.[8] In their study, pressures were usually low (less than 17 mm Hg in five of six patients) thus avoiding ischaemia of the oesophageal mucous membrane, but in one patient the pressure went up to 60 mm Hg, which is in the range of the arterial pressure routinely achieved during CPB. In the case we describe, the small build of the patient, the very long surgical procedure, and congestive right heart failure with low cardiac output, hypotension and high venous pressure during and after surgery (except during CPB) may have provided favourable conditions for an initial ischaemic injury of the oesophageal and tracheal walls. The low perfusion pressure of the mucosa as a result of low arterial and high venous pressures that were still present long after the removal of the probe prevented healing of the initial lesion. Although possible and described previously,[5] a thermal injury appears less likely as the echo transducer was disconnected during CPB and because of the security system of the echograph that turns off the transducer's power when its temperature exceeds 41°C.

One might argue that the tracheal tube or tracheal suction catheters could have been responsible for the complication. A lesion caused by the tracheal tube was discounted as tracheal intubation was easy and because systematic precautions are routinely implemented in our ICU to avoid and detect any displacement of the tube. Daily chest x-rays were performed and the tip of the tube was positioned normally on all images, several centimetres above the tracheal bifurcation. Other than the perforation itself, the tracheal surface was free of lesions suggesting that tracheal suctioning was performed atraumatically. The nasogastric tube was of small diameter, easily inserted and its correct positioning was verified on each chest x-ray.

The very severe multi-valvular heart disease of the patient, his poor preoperative condition, and the unusual duration of the procedure should have led us to alter our routine procedure of intraoperative TOE monitoring. Although the insertion of the probe before weaning of CPB is often more difficult than immediately after anaesthesia induction and tracheal intubation (interference with the surgical procedure, less easy use of a laryngoscope in case of unsuccessful blind insertion), we might have prevented this complication by removing the transoesophageal probe during CPB.

Guidelines have been published regarding the intraoperative use of TOE.[9] We performed TOE in this case in accordance with these recommendations. There were no contraindications to TOE in this case (in particular the preoperative oeso-gastro-duodenoscopy was normal) and no technical difficulty was encountered for insertion and positioning of the probe. However, we believe that very long TOE monitoring procedures in fragile patients should lead to increased precaution regarding the management of the echographic probe.

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Late oesophageal perforation after intraoperative transoesophageal echocardiography

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Serious haemodynamic instability occurred during emergency surgery for a perforated duodenal ulcer in a 72-year-old man with acute myocardial infarction. Intraoperative transoesophageal echocardiography was crucial for diagnosis of the location of myocardial infarction in the right ventricle and the subsequent haemodynamic management. Postoperatively, a thrombus in the right coronary artery was removed by coronary angiography. The patient's trachea was extubated on the fourth postoperative day. Another 4 days later a leak in the lower oesophagus was suspected because of pleural empyema, and verified. The patient's trachea had to be re-intubated and an oesophageal stent was inserted. The patient was discharged, fully recovered, 2 months after the operation.

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Keywords: complications, oesophageal perforation; heart; monitoring, transoesophageal echocardiography; gastrointestinal tract, oesophagus

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Transoesophageal echocardiography (TOE) is frequently used in cardiac and transplant surgery. TOE may also have a significant impact on intraoperative patient management in non-cardiac surgery.[1] We describe a late oesophageal perforation occurring after intraoperative TOE in a 72-year-old man with acute myocardial infarction undergoing emergency surgery for a perforated duodenal ulcer.

Case report

A 72-year-old male patient (170 cm; 125 kg; body mass index 43.3) attended our emergency room with upper abdominal pain, severe dyspnoea and circulatory shock (arterial pressure 80/60 mm Hg; heart rate 120 beats min^{-1}). He had a history of long-term use of non-steroidal anti-inflammatory medication. Suspected perforated duodenal ulcer was corroborated by intra-abdominal air on the computer tomogram and diffuse peritonitis. The ECG revealed acute inferior myocardial infarction, and this was confirmed by laboratory findings: troponin I, 45 μg litre^{-1} (normal value: <0.35 μg litre^{-1}); creatine kinase CK-MB enzyme activity, 396 U litre^{-1} (normal value: <25 U litre^{-1}); CK-MB mass, 313 μg litre^{-1} (normal value: <5.0 μg litre^{-1}). The patient had no chest pain.

Before inducing anaesthesia we inserted radial arterial, central venous and pulmonary artery catheters under local anaesthesia. Standard monitoring included ECG (five leads), pulse oximetry and capnometry. Anaesthesia was induced and maintained with midazolam, flunitrazepam, fentanyl and rocuronium. Immediately after induction, the patient's mean arterial pressure dropped to 35 mm Hg. Urgent vasoactive support with bolus injections and continuous infusions of epinephrine (0.16 μg kg^{-1} min^{-1}) and norepinephrine (0.12 μg kg^{-1} min^{-1}) was necessary to maintain arterial pressure. His heart rate increased to 140 beats min^{-1}, and cardiac output (8–10 litre min^{-1}), central venous pressure (16–20 mm Hg) and pulmonary artery pressure (45–65 mm Hg) were all above the upper normal limit. We decided to insert a TOE probe (multiplane 5 MHz probe, HP Sonos 1500; Hewlett-Packard, Andover, MA, USA) which was achieved without incident. The patient had a highly hypokinetic and dilated right ventricle, but good contractility of the left ventricle and a small endsystolic left ventricular volume. With on-line ultrasonographic control of right and left ventricular function, we undertook careful volume replacement using Ringer's lactate and a gelatine solution, and gradually reduced the rate of the catecholamine infusions. The patient's heart rate decreased to 90–100 beats min^{-1} while his mean arterial pressure was maintained at 70–80 mm Hg.

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At surgery, the abdominal cavity was found to be full of gastric juice and the peritoneal surface severely inflamed, with several areas of fatty tissue necrosis, which were confined to the vicinity of a perforated pyloric ulcer. The ulcer was excised, and a Heineke–Mikulicz pyloroplasty performed. The TOE probe remained *in situ* for about 2.5 h.

On postoperative day 1 the patient's haemodynamic status deteriorated. Because the right-heart failure was refractory to inotropic support, coronary angiography was performed. This revealed almost complete occlusion of the right coronary artery by a thrombus, which was removed. A temporary intra-aortic balloon pump was placed. In the following days the patient was successfully weaned from catecholamines and mechanical ventilation, and his trachea was extubated on postoperative day 4.

On postoperative day 5 a left-sided pleural effusion was identified on a chest radiograph, and then drained. On day 6, pulmonary function deteriorated rapidly and the patient's trachea had to be re-intubated. From day 5 onwards, neutrophil granulocytes increased significantly. An increase in C-reactive protein on the first two postoperative days was followed by a subsequent decrease, with a renewed increase on postoperative day 8. Pleural empyema was drained through a small thoracotomy. An oesophageal perforation was suspected when what appeared to be gastroenteral nutrition fluid was seen to issue from the thoracic drains. The leak in the lower oesophagus was verified by an upper gastrointestinal radiological contrast series (Fig. 1), which excluded other oesophageal lesions such as oesophageal stricture. We decided against a surgical repair of the leak, and inserted an oesophageal stent instead. The leakage then subsided, and the further postoperative course was uneventful. The patient was discharged from the ICU 8 weeks after surgery and was transferred to a rehabilitation centre 2 weeks later. He was discharged fully recovered 2 months later.

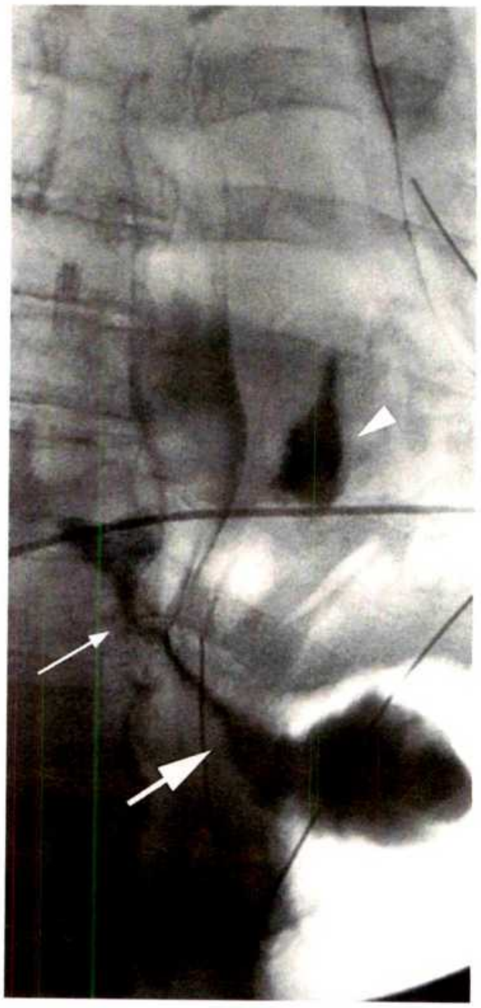

Fig 1 Perforation of the distal oesophagus identified by the extravasation of water-soluble contrast agent (thin arrow). Arrowhead: extraluminal contrast agent in the dorsal mediastinum; large arrow: cardia.

Discussion

While serious oesophageal lesions associated with the use of TOE are rare, reports have been increasing.[2–7] To date, eight cases of serious oesophageal perforation occurring during TOE have been reported. Five of these eight perforations occurred during insertion of the TOE probe, and the lesion was located in the hypopharynx or the proximal oesophagus.[2 5–7] Only a single case of lower oesophageal perforation had been described, which was not caused during insertion of the probe, but occurred intraoperatively while the probe remained *in situ*.[8]

The aetiology in our patient may be different. TOE probes can exert pressures of up to 60 mm Hg, with the potential to cause mucosal ischaemia.[9] In addition, perfusion of the oesophageal mucosa in our patient may have been impaired by prolonged cardiovascular instability with low arterial pressure, which may have significantly contributed to the oesophageal lesion.

In contrast to Kharasch and colleagues[8] we observed a significantly longer interval between the lesion induced by the TOE probe and the first symptoms of perforation (6 days *vs* a few hours). The reason for the delay in clinical symptoms in our pateint is not clear, but may be related to delayed enteral nutrition. Because of the late presentation of the oesophageal perforation, we refrained from surgical repair.[10 11] The mortality rate from iatrogenic oesophageal perforation is high, and early diagnosis and treatment significantly improve the prognosis. Three of the five patients with oesophageal TOE perforation died.[2 5–8] The overall mortality rate for oesophageal perforation varies from 10% to 25%.[3]

It is highly unlikely that the oesophageal lesion had already been present, and was not caused by the TOE probe. The incidence of oesophageal ulcers or perforations in the absence of Boerhaave's syndrome or a carcinoma is extremely low, and the concurrence of such an oesophageal lesion with a duodenal ulcer is even lower.[12]

The use of TOE in patients with known gastro-oesophageal diseases such as strictures, burns, cancer or diverticuli, or in patients undergoing irradiation therapy or gastroduodenal ulcer therapy is not recommended.[8 13] Oesophageal varices are only a relative contraindication, because TOE is often used during liver transplantation in patients with end-stage liver disease and oesophageal varices. In our case we used TOE because the information provided by the Swan–Ganz catheter with continuous measurement of cardiac output and mixed oxygen saturation was inconclusive. TOE revealed the location of the myocardial infarction in the right ventricle, the low left ventricular preload and good left ventricular contractility.

In conclusion, TOE may provide crucial information in patients with relative contraindications and thus may be used in life-threatening situations. However, impaired mucosal perfusion because of cardiovascular instability appears to be an important risk factor for late oesophageal TOE perforation.[8]

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Oxygen embolism after hydrogen peroxide irrigation of a vulvar abscess

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We report a case of venous oxygen embolism in a 33-yr-old healthy woman after irrigation of a vulvar abscess with 25 ml of 3% hydrogen peroxide. Venous oxygen embolism was diagnosed by the development of sudden hypoxia associated with a decrease in end-tidal carbon dioxide concentration from 5.3 kPa to 3.2 kPa, and a 'mill-wheel' sound on cardiac auscultation soon after injection of the solution. The patient responded to corrective treatment including the Trendelenburg position and 100% oxygen. She made an uneventful recovery. We discuss the possible causative mechanism of this embolism, the different diagnostic methods, and the controversial aspects of available treatments. We emphasize that hydrogen peroxide is a dangerous and unsuitable agent for routine wound irrigation and debridement.

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Hydrogen peroxide (H_2O_2) is commonly used for the treatment of abrasions, superficial wounds and abscesses. The release of effervescent oxygen bubbles and their oxidizing effects on bacteria and viruses,[1] are normally considered as effective methods for the mechanical removal of any contaminant. However, despite its apparently harmless mechanism of action, H_2O_2 has been implicated in several fatal or near-fatal complications.[2–6] Injected into enclosed body cavities or open wounds, H_2O_2 can provoke venous and arterial oxygen embolism. We describe a case of venous oxygen embolism which occurred during drainage of an infected cyst of the labia majora. This is the first report of an oxygen embolism occurring during a gynaecological surgical procedure.

Case report

A 33-yr-old healthy woman was admitted during the night with a large and painful abscess of the right labia majora. In the morning, after midazolam 7.5 mg (oral premedication), she was taken to the operating theatre. Monitoring included ECG (lead II), non-invasive arterial pressure, pulse oximetry and capnography. Anaesthesia was induced with propofol 150 mg and alfentanil 500 µg and maintained with 1.5–2.5% sevoflurane, 40% oxygen, and nitrous oxide. The patient was breathing spontaneously *via* a face mask. The initial oxygen saturation (Sp_{O_2}) was 100% with an end-tidal carbon dioxide tension (PE'_{CO_2}) of 4.9 to 5.3 kPa. A purulent collection was drained out of the mass and 25 ml of a 3% hydrogen peroxide solution was syringed under pressure into the abscess. Vigorous bubbling was seen at the cavity opening.

Approximately 2 min later, the Sp_{O_2} decreased rapidly to 89% and the PE'_{CO_2} to 3.2 kPa, without any change in arterial pressure or pulse rate. To ensure adequate ventilation, the patient was given succinylcholine 75 mg, intubated and manually ventilated.

The anaesthetic and breathing system were immediately checked to exclude any malfunction. On auscultation of the lungs, nothing abnormal was detected, but a 'mill-wheel' sound could be heard on auscultation of the heart. The patient was placed in the Trendelenburg position, anaesthetic gases were discontinued and 100% oxygen was administered. Haemodynamic variables remained normal The operation ended quickly, and after a few minutes the 'mill-wheel' murmur could no longer be detected. Sp_{O_2} and PE'_{CO_2} returned to their preoperative values and the patient was extubated without incident. Arterial blood gas analysis showed pH 7.32, Pa_{O_2} 12.2 kPa and Pa_{CO_2} 6.7 kPa on a FI_{O_2} of 0.4.

A chest radiograph, an electrocardiogram and a 2D transthoracic echocardiography were performed within 30 min of the incident. They were all normal. A second chest radiograph and a ventilation/perfusion lung scan were performed a few hours later and failed to demonstrate any sign of aspiration or pulmonary thromboembolism.

After close observation in the recovery room for 24 h, the patient showed no signs of any pulmonary complication and was discharged home.

Discussion

H_2O_2 rapidly decomposes to water and oxygen,[1] and is therefore often considered to be a harmless and user-friendly antiseptic and cleansing agent. However, since 1 ml of 3% H_2O_2 produces 9.8 ml oxygen, serious complications can arise if this is liberated in the vascular bed.

How such oxygen bubbles enter the capillaries remains unclear. In one study,[7] it was suggested that the high heat of decomposition of H_2O_2 favoured tissue disruption and enabled oxygen bubbles to penetrate into the vascular bed. But in another study,[8] the authors noted that subcutaneous injection of two or three times the volume of gaseous oxygen produced by a lethal dose of H_2O_2 was possible without killing laboratory rats. The authors concluded that embolization was caused by oxygen bubbles being released within the vascular bed by absorbed H_2O_2, rather than by penetration of the capillaries by gaseous oxygen. This may explain why many reports underline the danger of injecting H_2O_2 under pressure in closed or semi-closed cavities.[3 5 6] It may force H_2O_2 into blood vessels, rapidly producing critical amounts of gaseous oxygen. In our case, 25 ml of 3% H_2O_2 was probably sufficient to trigger a venous gaseous embolism, since it was injected under pressure into a semi-closed space which has extensive venous drainage.[9]

Once produced, the venous oxygen bubbles are carried to the right heart where they can impede cardiac output, or are trapped in the lungs, with a spatial distribution depending on their buoyancy and the flow dynamics within the pulmonary circulation.[10] If the lungs are severely overloaded with gas, bubbles may also pass through the pulmonary filter and increase the likelihood of coronary or cerebral vascular obstruction.[11]

Early diagnosis of venous gas emboli can be made by precordial Doppler, transthoracic and transoesophageal echocardiography, the latter detecting as little as 0.02 ml

kg^{-1} of air.[12] Less sensitive are the presence of a decreased $P\text{E}'_{CO_2}$, an increased mean pulmonary arterial pressure, a 'mill-wheel' murmur, hypoxaemia, hypercapnia and hypotension.[12 13] In our case, the diagnosis was made by the presence of sudden and reversible hypoxaemia associated with a decreased $P\text{E}'_{CO_2}$ and a transitory mill-wheel sound on cardiac auscultation, soon after application of H_2O_2.

Most cases[14] of gas embolism involve air (neurosurgical procedures, central venous lines, diving, extracorporeal circulation), or carbon dioxide (laparoscopic procedures). The usual preventive measures and treatments for air embolism are also recommended for oxygen embolism. They include flooding the wound with saline, increasing right atrial pressure by military antishock trousers, or positive end-expiratory pressure ventilation and avoiding volume depletion.[4] If an embolism is suspected or detected, it is recommended that the patient is placed in the Trendelenburg position to entrap bubbles in the right ventricle and reduce the rate of embolization.[2] However, in the presence of a patent foramen ovale which is present in 25–30% of the population, increased right atrial pressure can cause arterial embolization. Further treatment includes aspiration of gas from the right side of the heart through a central venous line, and discontinuation of nitrous oxide (N_2O).[2 3] In the event of cardiovascular collapse, cardiopulmonary resuscitation should be initiated. Finally, if neurological damage following arterial gas embolism is diagnosed, hyperbaric oxygen therapy is suggested.[15]

However, if we consider specifically embolism due to oxygen and H_2O_2, some of these measures may be regarded as controversial. For instance, since H_2O_2 might be partially forced into the vascular bed at the time of injection and before it vaporizes,[8] flooding the wound with saline will not prevent the risk of gas entrapment within the capillaries.

As N_2O is more soluble in plasma than oxygen, stopping the N_2O and ventilating the lungs with 100% oxygen is also recommended to prevent any oxygen bubble expansion. But one of the most likely mechanisms of gas elimination is molecular diffusion directly across the arteriolar wall into the alveolar spaces, which depends on the existence of a partial pressure difference between the capillaries and the alveoli.[16 17] In the case of oxygen bubbles within the pulmonary circulation, if 100% oxygen is applied to the alveolar space, the partial pressure difference theoretically falls to zero, preventing any excretion. As most patients treated with 100% oxygen have, however, recovered without long-term complications after oxygen emboli, there are probably other mechanisms of elimination such as metabolism and absorption, mainly in peripheral tissues. Ventilating the lungs with 100% oxygen can still be considered necessary, since the cause of the hypoxia and fall in $P\text{E}'_{CO_2}$ may not always be clear initially.

We conclude that hydrogen peroxide is a potentially dangerous substance, particularly when applied to vascular closed cavities. The risk of oxygen embolization together with its tendency to cause oxidative tissue damage makes it an unsuitable agent for routine wound debridement.

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Anaphylaxis to rocuronium

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Reports about anaphylactic and anaphylactoid reactions to rocuronium have increased recently. We report two new cases of documented grade III anaphylaxis, leading to death in one patient. The first case occurred in an 81-year-old ASA II woman scheduled for emergency abdominal surgery. Severe hypotension and tachycardia were observed after rocuronium, without bronchospasm. Neosynephrine allowed rapid resuscitation, and the patient recovered fully. The second patient was a 64-year-old ASA II man scheduled for abdominal surgery. Severe haemodynamic instability and bronchospasm occurred after rocuronium. Despite immediate life support, the postoperative period was complicated by persistent low systolic pressure, acute respiratory distress syndrome, acute renal failure, disseminated intravascular coagulation and pancreatitis, leading to the death of the patient.

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Rocuronium has been available in France since 1994. It is a widely used aminosteroidal non-depolarizing neuromuscular blocking agent that shares many pharmacological features with vecuronium. It has the advantage of a more rapid onset time,[1] which has led many anaesthetists to use rocuronium rather than vecuronium.[2] Case reports,[3–12] and correspondence,[13–14] about both anaphylaxis (characteristic clinical symptoms, positive allergological tests) and anaphylactoid reactions (unusual clinical symptoms and reaction not mediated by IgE) after rocuronium have increased recently. Such reactions are often life-threatening and may be fatal.[1–14] One fatality following rocuronium has already been reported.[2] We report two new cases of documented grade III anaphylaxis, leading to death in one patient.

Case reports

Case 1 was an 81-year-old ASA II woman scheduled for emergency abdominal surgery in March 2000. Her past medical history included a nervous breakdown and atrial fibrillation. Her medication consisted of fluoxetine and verapamil. She had previously undergone eight general anaesthetic procedures, including orthopaedic (knee and hip) surgery, and repair of a genital prolapse. Induction was achieved with thiopental 350 mg and succinylcholine 80 mg. Following loss of consciousness, the trachea was intubated. Twenty min later and before skin incision, rocuronium 30 mg and sufentanil 10 µg were administered. One min later, the patient exhibited narrow complex tachycardia (156 beat min^{-1}), severe hypotension (45/32 mm Hg), and weak chest erythema, but did not develop bronchospasm. Incremental doses of neosynephrine up to 200 µg were given, and both heart rate and arterial pressure returned to basal values. Because of the rapid resuscitation, surgery was not cancelled. After surgery, the patient was transferred to the recovery room and her trachea was extubated 1 h later. She recovered fully and was discharged 6 days later.

Blood samples obtained at 30 min and 1 h, and urine sampled at 3 h after the reaction demonstrated increased levels of histamine (19.7 and 6.7 nmol ml^{-1}, respectively; normal value <6 nmol ml^{-1}), and tryptase (27.9 and 19.2 nmol ml^{-1}, respectively; normal value <13.5 nmol ml^{-1}) but normal urinary methylhistamine. Specific IgE antibodies against quaternary ammonium ions and rocuronium measured during the reaction were negative. Cutaneous tests were performed by an allergologist 6 weeks later. Skin-prick testing produced wheals <3 mm in the negative control and 10×8 mm in the positive (codeine sulfate) control. Skin-prick testing confirmed the diagnosis of anaphylaxis to rocuronium (8×7 mm). A positive skin test was also

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observed with the other aminosteroidal neuromuscular blocking agents (pancuronium: 9×10 mm; vecuronium: 8×9 mm), but not with the benzylisoquinolinium neuromuscular blocking agents (<3 mm). Intradermal tests were positive to rocuronium (1:100 dilution),[16] with a wheal of 11.5 mm and flare of 35 mm, but negative to succinylcholine (1:10 dilution).

Case 2 was a 64-year-old ASA II man scheduled for hernia repair in November 2000. Previous general anaesthesia for umbilical hernia repair and melanoma resection had been uneventful. His medical history included venous thromboembolism and obesity and he was treated with oral anticoagulants (acenocoumarol). Anaesthesia was induced with sufentanil 15 µg and propofol 400 mg. Following loss of the eyelash reflex, rocuronium 50 mg was administered and the trachea was intubated. Shortly after rocuronium administration, the patient developed bronchospasm, hypotension (50/30 mm Hg), tachycardia (135 beat min^{-1}), and generalized erythema. The patient was resuscitated with epinephrine (up to 2 mg i.v., followed by a continuous i.v. infusion of 0.5 mg h^{-1}), hydrocortisone 200 mg and colloid 2 litres i.v. Surgery was cancelled and the patient was transferred to the intensive care unit. The postoperative period was complicated by persistent low systolic arterial pressure, acute respiratory distress syndrome, acute renal failure, disseminated intravascular coagulation and pancreatitis, leading to death 7 days later.

Blood samples obtained at 30 min and 1 h, and urine sampled at 3 h after the reaction demonstrated elevated levels of histamine (>100 and 44.6 nmol ml^{-1}, respectively; normal value <6 nmol ml^{-1}), mast cell tryptase (>200 nmol ml^{-1} for both blood samples; normal value <13.5 nmol ml^{-1}) and urinary methylhistamine (10 318 nmol litre^{-1} or 849 nmol mmol creatinine^{-1}; normal value <170 nmol mmol creatinine^{-1}), in keeping with anaphylaxis. Specific IgE antibodies against quaternary ammonium compounds were detected (QAS-radioimmunoassay technique: 3.5%) with positive radioimmunoassay inhibition by rocuronium (63%).[15]

Discussion

We report two more anaphylactic reactions to rocuronium, leading to the death of one patient. According to the Ring and Messmer classification, these two cases were considered to be grade III.[17]

In the first case, the patient did not exhibit any reaction when she received succinylcholine whereas 20 min later, she developed an anaphylactic reaction immediately after rocuronium. Skin tests were highly positive (1/100) to rocuronium, but negative to atracurium, a well-known histamine-releasing drug, suggesting an IgE-mediated reaction. The patient may have been previously sensitized to steroidal neuromuscular blocking agents (she had already undergone eight general anaesthetic procedures), without cross-reactivity to atracurium or succinylcholine. Specific IgE antibodies against quaternary ammonium ions were negative. This negative result is not rare, as IgE may have been consumed during the reaction. The technique has only 85% sensitivity.[15] Therefore, the lack of specific IgE detection during such an adverse effect does not rule out an anaphylactic origin.

In contrast, there is no doubt that the second case documents a typical anaphylactic reaction because of the clinical presentation and the increase in mast cell tryptase and specific IgE antibodies against rocuronium. Despite rapid resuscitation, the patient died after developing multiple organ failure. Such a fatal event has already been described with rocuronium and has been documented with other neuromuscular blocking agents.[2]

The use of rocuronium is increasing and it is not surprising that reports of side-effects such as anaphylaxis increase concomitantly.[2–14] A high 'rocuronium-mediated anaphylaxis rate' is suspected by some authors,[2 9–11] who recommended close monitoring of such adverse events. We agree with this recommendation. We would like also to emphasize that neuromuscular blocking agents are the main drugs responsible for life-threatening episodes during anaesthesia, but such agents are not always necessary surgically. There are several studies of the ability to intubate without neuromuscular blocking agents.[18] Between 1995 and 2000 the use of muscles relaxants in intubated patients decreased from 100% to 25% in our institution, without any related adverse events. We believe full reporting is important to study the potential risks of anaphylaxis to rocuronium.

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Correspondence

Serotonin toxicity and malignant hyperthermia: role of 5-HT$_2$ receptors

Editor—We congratulate the authors on an excellent review of aspects of the pathophysiology of malignant hyperthermia (MH).[1] They have explained the postulated role of serotonin in MH, in particular the role of peripheral 5-HT$_2$ receptors, based on *in vitro* and *in vivo* animal work. There are important parallels between serotonin toxicity and MH, and this review adds to our understanding of the role of 5-HT$_2$ receptors, peripheral and central, in both serotonin toxicity and MH. There is recent animal work that has defined the role of 5-HT$_{2a}$ receptors in serotonin toxicity,[2] and reports of the use of 5-HT$_2$ antagonists in the treatment that should make us rethink the conventional descriptions of serotonin toxicity, which were restated by Wappler and colleagues.[1]

Serotonin syndrome, better described as a spectrum of toxicity than a distinct syndrome, is characterised by:

(i) neuromuscular hyperactivity—hyperreflexia, clonus, myoclonus, tremor and rigidity;
(ii) autonomic hyperactivity—hyperpyrexia, tachycardia and diaphoresis; and
(iii) altered mental status—agitation, anxiety, hypomania and confusion.

While there are some similarities with neuroleptic malignant syndrome, the time course, neuromuscular features and autonomic features are usually quite distinct.[3] Malignant hyperthermia is also a distinctly different condition, but some of the peripheral and autonomic features that occur with severe serotonin toxicity more closely resemble MH. This raises the possibility that peripheral 5-HT$_2$ receptors are involved in both conditions.

Recent studies implicate 5-HT$_{2a}$ receptors in the pathophysiology of serotonin toxicity, not the 5-HT$_{1a}$ receptor which was initially thought to be involved.[4] These studies have used an animal model of serotonin toxicity where rats were administered clorgyline, a monoamine oxidase inhibitor (MAOI), and 5-hydroxyl-L-tryptophan (5-HTP).[5] In the control group, the temperature increased to more than 40°C, and the rats exhibited behavioural changes including tremor, and died within 75 min. Animals pretreated with the potent 5-HT$_{2a}$ antagonist, ritanserin, and the atypical antipsychotic risperidone which has strong 5-HT$_{2a}$ blocking action, had no rise in temperature, no behavioural changes and all survived.[2,5] Animals pretreated with high dose chlorpromazine and cyproheptadine, both 5-HT$_2$ antagonists, all survived and had a suppression of the temperature rise. However, pretreatment with propranol, 5-HT$_{1a}$ receptor antagonist (as well as a beta blocker), dantrolene and haloperidol did not prevent death in any of the animals, although the first two drugs did suppress the rise in temperature to some extent.[2,5]

The lack of effect of dantrolene in these two studies[2,5] suggests that peripheral muscle effects play a lesser role in serotonin toxicity compared to MH, where dantrolene is more effective.[1] The studies also do not support the use of propranolol or haloperidol in the treatment of serotonin toxicity. Clinical studies do, however, support the use of 5-HT$_2$ antagonists, such as cyproheptadine, in the treatment of serotonin toxicity.[6]

The animal studies described by Wappler and colleagues[1] also raise the possibility that peripheral 5-HT$_2$ receptors may be involved in serotonin toxicity. In our experience, the main features of mild to moderate serotonin toxicity are hyperreflexia, clonus, tremor and autonomic features, with rarely any mental state changes. These neuromuscular features are similar to those described in the animal studies quoted by Wappler and colleagues[1] which were elegantly demonstrated to be due to peripheral 5-HT$_2$ receptor effects. Thus, neuromuscular features are an intrinsic part of serotonin toxicity, although whether this is mediated only *via* central 5-HT$_{2a}$ receptors or peripheral 5-HT$_2$ receptors is unclear.

In severe serotonin toxicity, which occurs almost exclusively when MAOIs (including reversible inhibitors of monoamine oxidase) or serotonin-releasing agents (e.g. MDMA or ecstasy) are combined with a selective serotonin reuptake inhibitor (SSRI), the condition is even more like MH with severe hyperpyrexia, rigidity and hypercapnia, requiring paralysis and sedation for effective management Rhabdomyolysis and increased creatine kinase can also occur. Peripheral 5-HT$_{2a}$ receptors in skeletal muscle may be involved in these severe cases, resulting in a picture similar to MH.

Serotonin toxicity is becoming increasingly common in many situations in medicine. It commonly occurs in overdoses of serotonergic agents, and drug interactions continue to be a problem. This can be a problem in perioperative patients, where a number of analgesics can induce serotonin toxicity in patients already taking SSRIs. The most important is pethidine, which is well reported as causing serotonin toxicity in patients on SSRIs.[7] Tramadol may also be a problem,[8] particularly in patients requiring longer term pain management. Thus, in the post-operative period, there is the possibility of both serotonin toxicity and MH occurring. Careful clinical assessment is needed to distinguish between these possibilities and allow appropriate treatment to be given.

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Editor—We wish to thank Isbister and Whyte for their interest in our review and their contribution to this debate. The main problem in interpreting the results from animal studies using the established MH pig model is whether MH-like episodes, following administration of 5-HT$_{2A}$ receptor agonists, are 'true' MH or are due to other mechanisms like the serotonin syndrome.

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Three underlying pathways might be responsible for the MH-like signs and symptoms after administration of 5-HT$_{2A}$ agonists in conscious pigs. First, substance-specific direct effects at peripheral sites (i.e. an activation of the skeletal muscle cell *via* 5-HT$_{2A}$ receptors resulting in a MH crisis) could be responsible for the clinical presentation. This hypothesis has been proved using the *in vitro* contracture test model.[1] The *in vitro* results demonstrated that the 5-HT$_{2A}$ receptor agonist, DOI, induced contractures in skeletal muscle specimens from both MH susceptible (MHS) and normal (MHN) patients, indicating a direct serotonergic effect on skeletal muscles.[1] Furthermore, the onset of contracture development was significantly faster and more intense in MHS compared to MHN sample. Pretreatment with DOI led to an accelerated and increased contracture development following halothane administration in specimens from MHS but not MHN patients. The *in vitro* effects of 5-HT$_{2A}$ receptor agonists on muscle specimens from MHS patients could be reduced or completely counteracted by dantrolene, as well as with the 5-HT$_2$ receptor antagonist, ritanserin. In subsequent experiments, ritanserin was shown to inhibit halothane-induced contractures in MHS muscles in a concentration-dependent manner. However, compared to the established triggering agents, halothane, ryanodine and 4-chloro-*m*-cresol,[2,3] the contracture development in MHS preparations after DOI was prolonged and of only moderate intensity.

Second, a porcine stress syndrome might be induced after administration of 5-HT$_{2A}$ agonists in susceptible pigs. This syndrome describes MH susceptible animals which are adversely affected by stress induced by isolation, trucking, weaning, fighting, coitus and crowding.[4] Clinical signs and symptoms are exactly comparable with a MH crises induced by anaesthetic agents, and therefore the porcine stress syndrome is interpreted as a stress-induced MH. But hallucinogen-induced psychosis in conscious pigs might lead to a central stress situation, which secondarily results in the MH-typical pathomechanisms in skeletal muscles.

The third theory focuses on a 5-HT$_{2A}$ specific central agonism, which was recently described as serotonin syndrome. It is caused by excessive 5-HT availability in the central nervous system at the 5-HT$_{1A}$ receptor, distinct from possible interactions with 5-HT$_2$ and dopamine receptors This syndrome can be initiated by serotomimetic medication in combination with 5-HT, or by an increase in dosage of serotomimetic drugs, leading to excessive elevation of intrasynaptic 5-HT levels. Clinical signs and symptoms include rapid onset of cognitive-behavioural alterations (agitation, confusion and disorientation), neuromuscular abnormalities (rigidity, tremor and myclonus), and dysfunction of the autonomic nervous system (fever, tachypnoea and altered blood pressure). Although the clinical presentations are similar, there is a differing severity between classic MH and serotonin syndrome.

Although the results from recent studies are interesting,[5,6] a clear differentiation between MH and the serotonin syndrome cannot be drawn from these experiments First, the authors used rats in their model and a MH disposition has not been demonstrated in these animals. Second, Löscher and colleagues[7] investigated conscious pigs in their studies.[4] This study design enabled the induction of MH by psychomimetics but, as mentioned above, this might be due to porcine stress syndrome.

It would, therefore, be worthwhile to investigate the *in vivo* effects of 5-HT$_{2A}$ receptor agonists on anaesthetized MHS and MHN swine. In such an experimental setting, a hallucinogen-induced stress reaction would be excluded and a differentiation between MH and serotonin syndrome would be possible. Furthermore, we agree with the suggestions made by Isbister and Whyte that beside experimental settings, careful clinical assessment of mechanims leading to a serotonin syndrome and/or MH are needed in order to allow appropriate treatment in such cases.

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Anaphylaxis during anaesthesia

Editor—We read with interest the article by Laxenaire and colleagues[1] concerning the French survey of anaphylaxis during anaesthesia In this retrospective study, most of the reactions were attributed to neuromuscular blocking drugs or latex, and the authors claim that succinylcholine and rocuronium are responsible for more accidents than expected. There are several reasons to be cautious about the interpretation of this data.

(i) The present survey, like others,[2,3] is based on case reports. According to guidelines for grading the quality of evidence,[4,5] case reports, even numerous (n=477 in the present survey), have the lowest level of scientific relevance (grade V). In epidemiology, an association between an event (i.e. anaphylaxis) and a battery of tests (i.e. skin and blood tests) is demonstrated through case–control studies. Thus it is necessary to include a control group made up of patients exposed to the products incriminated but who did not develop any anaphylactic reaction and who also underwent blood and skin tests. The authors of the present article[1] do not mention any data on the specificity of these tests.

(ii) To determine the incidence of an event, one requires a numerator and a denominator. The denominator (i.e. the number of patients exposed to muscle relaxants during anaesthesia in France) can be estimated from a 1996 survey of anaesthesia in that country.[6] According to that study, five million patients received muscle relaxants during a 2-yr period. The value of the numerator is more difficult to obtain. Only patients having clinical features of anaphylaxis confirmed by true positive tests should be counted. However, the authors of this study do not provide any information about the number of true and false positives Assuming that all cases reported are true positives, the incidence can be estimated to be 336 per 5 000 000 patients exposed to muscle relaxants (approximately 1:15 000), or 1:312 000 when taking account of only severe, grade IV (4.9%[1]) reactions.

(iii) Ninety-eight patients were suspected of developing an anaphylactic reaction to rocuronium, but only 77 skin tests were performed.[1] Six of these tests were done using a 10^{-1} dilution, which can yield non-specific responses according to the results of Levy and colleagues.[7] Thus one can assume that 10% of patients receiving rocuronium and developing clinical signs of an anaphylactic reaction had false positive skin tests, suggesting that the incidence of a rocuronium-induced anaphylactic reaction is overestimated in the present study.[1]

(iv) The clinical manifestations of an anaphylactic reaction (cutaneous signs, hypotension, tachycardia, and/or bronchospasm) are non-specific, so reporting might be modulated by the clinician's perceived likelihood that a drug might produce such reactions. Thus data on the sensitivity and specificity of the tests are required.

(v) To determine a relative risk of anaphylaxis based on estimated sales of muscle relaxants and to apply a statistical anaylsis to the results is very hazardous at best. Some patients receive more than one vial, muscle relaxants are also used outside the operating room (e.g. intensive care unit, emergency unit), some vials are not used (e.g. broken, lost, expired), and the contents of multidose vials might be given to different patients. This kind of calculation might lead to completely erroneous numbers. For example, Rose and colleagues[8] conclude that rocuronium is not associated with an increased risk anaphylaxis, contrary to what is suggested by Laxenaire and colleagues.[1]

(vi) For this type of investigation, it is essential to distinguish between the individual and the population. For a patient who has had a positive reaction to a certain agent, it is prudent to avoid the drug in a future anaesthetic. However, even if the tests are positive, this does not constitute proof that the suspected drug is reponsible for the observed symptoms, especially if they are not specific. In a given population, a high incidence of a positive test concerning a drug does not mean that the agent will trigger symptoms in these patients.

(vii) Paradoxically, atracurium and mivacurium, which are known to produce dose-dependent histamine release, were not incriminated often. As the manifestations of anaphylactoid and true anaphylactic reactions are similar, it is possible that cases involving these agents were under-reported, as the symptoms were likely to be interpreted as an expected side-efffect.

In conclusion, there is no evidence to support the belief that anaphylactic reactions with succinylcholine and rocuronium are more frequent in France than in other countries, and these events are very rare. Moreover, in the absence of a personal history, it would be ill advised to choose one muscle relaxant over another or to avoid muscle relaxants altogether solely on the basis of their alleged allergic potential.

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Editor—Thank you for the opportunity to respond to the remarks of Plaud and colleagues concerning our article.

Our study concerns a collection of cases of anaphylaxis occurring during anaesthesia, recorded consecutively over a 2-yr period by the GERAP, a nation-wide network of 38 French allergo-anaesthesia outpatient clinics. As in many countries, these data are based on a system of reporting by practitioners who observed anaphylactoid reactions during anaesthesia and then referred the patients for allergy investigations. In the case of rare, random, independent adverse reactions, such as immune-mediated anaphylactic reactions, epidemiological surveys do not usually involve a control group. However, the sample size of such observational studies is of crucial importance Pharmacovigilance reports, as in this study, should not be considered as a simple collection of individually published case reports with the lowest level of scientific evidence (grade V). These pharmacovigilance reports are more likely to be considered as large series of well-defined patients undergoing standardized investigations Such series, which have not been defined in the classification established by Cook,[1] are considered as studies of grade III level of scientific evidence by the French Society of Anaesthesiology [2]

The sensitivity of skin tests to neuromuscular blocking agents is estimated at 94%.[3] Their specificity must be considered relative to the dilutions used and has been evaluated at 97%.[4] The sensitivity and specificity of specific IgE assay against muscle relaxants have been shown to vary from 88 to 97% and 97 to 100%, respectively.[5,6] However, the positive predictive value of these tests will be very different in groups with a highly different prevalence of anaphylaxis. It has been estimated at 71% for a specific IgE assay against muscle relaxants in a selected population of patients who have experienced an anaphylactoid reaction during anaesthesia, but will only be 0 11% in control subjects.[7] Similarly, the positive predictive value of skin tests in normal subjects could be estimated at 0.3%.[8] For these reasons, the use of such tests for muscle relaxant sensitivity screening, prior to surgery, is not advisable.

As stated by Plaud and colleagues, the incidence of anaphylaxis remains difficult to determine. Among the many potential problems of the surveillance of adverse reactions, they emphasize the neccessity to avoid false positives. However, one should keep in mind that one of the major problems encountered is under-reporting of adverse drug reactions, which has been evaluated at 40% in France.[9] For these reasons, we did not perform any estimation of the incidence of anaphylaxis in our report Moreover, to estimate the incidence of severe anaphylaxis, they take into account only grade IV reactions (cardiac arrest, 4.9% of our cases). However, grade III reactions (67.1% of our cases), which are also life-threatening, are severe reactions, and therefore must also be considered.

Concerning the 98 patients allergic to rocuronium, skin tests were found to be positive in all subjects: prick tests in 21 patients, and intradermal tests in 77 patients. A prick test, carried out with undiluted drug is considered to correspond with an intradermal test using a 10^{-3} dilution.[10] Notwithstanding the results reported by Levy and colleagues in healthy volunteers,[11] in our six cases where positivity of the intradermal test was observed at a 10^{-1}

dilution, specific IgE assay against rocuronium was positive. These results confirm the responsibility of this agent for the adverse reaction observed.

As mentioned in our report, we agree that the number of patients exposed to the various neuromuscular blocking agents was based on the estimation of the market share of these agents and should therefore be considered with circumspection. Nevertheless, as specified in the method section, this estimation concerns the consumption of each neuromuscular blocking agent effectively used during anaesthesia and not the vials used in intensive care units or in emergency settings (data obtained from Le Panel Hospitalier, MAPI, Lyon, Edition Domaine Médical, 1998). In addition, a correction factor, which took into account the average number of vials of a specific neuromuscular blocking agent used during a standard anaesthetic procedure, was applied. This correction factor was established in accordance with Glaxo Wellcone and Organon Teknika for the products they sold. Finally, the number of vials not used (e.g. broken, lost, expired) will not be different for the various muscle relaxants, and the use of multidose vials for different patients is not authorized in France.

Plaud and colleagues stated that there is no evidence to support the belief that anaphylactic reactions to succinylcholine and rocuronium are more frequent in France than in other countries, and that these events are very rare. We completely agree with this statement. Indeed, in previous reports from our group and others the estimated incidence of anaphylaxis was 1 in 10 000 to 1 in 20 000 in Australia in 1993,[12] and 1 in 13 000 in France in 1996[9] In the series of 24 cases recently published by Rose and Fisher[13] from Australia, the incidence of rocuronium allergy increased in parallel with national sales. However, one third of the cases of anaphylaxis to rocuronium (n=10), which fulfilled all the criteria, were not included in the estimation of this incidence, because they were investigated in another centre, Thus, the Australian report concerns results from a single centre (Sidney), whereas our data are obtained from a nationwide network of allergo-anaesthesia outpatient clinics. In addition, based on data from intradermal testing, as in our report, some unexplained differences between drugs were observed by Rose and Fisher. These unexpected differences, led these authors to consider rocuronium as a neuromuscular blocking agent at intermediate risk of sensitization, when compared with low-risk agents (e.g. pancuronium, vecuronium) and high-risk agents (e.g. succinylcholine, alcuronium).

We agree that a positive skin test for a drug does not mean that the agent will trigger symptoms in a patient. The only way to definitely establish the responsibility of the suspected drug will be to reintroduce it, but this is not ethically possible.

Finally, Plaud and colleagues raise the problem of possible under-reporting or bias-reporting of adverse reactions, especially concerning known histamine-releasing drugs. However, one should note that patients are referred to our centres by anaesthetists after an anaphylactoid reaction, independently of the anaesthetic protocol used and/or the severity of the reaction Above all, they want to know the mechanism of the reaction, and in the case of anaphylaxis, the incriminated agent (neuromuscular blocking agent, latex, antibiotics, colloids etc). This is illustrated by the high proportion of mild immue-mediated adverse reactions to atracurium reported in our study, as shown in Table 1.

Table 1 Clinical severity of anaphylaxis to neuromuscular blocking agents collected in France in 1997–8 (n=333)

Neuromuscular blocking agents	Number of patients	Clinical grade of severity			
		I	II	III	IV
Atracurium	71	9	17	41	4
Rocuronium	98	4	20	72	2
Succinylcholine	78	3	8	58	9
Vecuronium	59	4	20	34	1
Pancuronium	18	0	1	15	2
Mivacurium	9	2	3	4	0

Surveillance of adverse reactions represents a methodological problem and a statistical challenge. For these reasons, we never recommend one muscle relaxant over another, or avoiding muscle relaxants on the basis of their allergic potential. On the contrary, we advocate the need for post-marketing risk surveillance, investigation of adverse reactions, and training of anaesthetists in the diagnosis and treatment of potentially life-threatening anaphylactic reactions.

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Receptive site topology of the acetylcholine receptor

Editor—I read with interest the review article by Lee,[1] which represents an important addition to the field of clinical neuromuscular pharmacology. I noted, however, that the acetylcholine receptor structure presented by Lee (both in Figure 2 and in the text) represents the fetal form (containing a γ rather than an ε subunit).[2 3] We now know that the nicotinic acetylcholine receptor (nAChR) of adult mammalian skeletal muscle is a pentameric complex of 2 α subunits in association with a single β, δ, and ε subunit We also know that the fetal type nAChRs are resistant to nondepolarizing neuromuscular blockers are more sensitive to succinylcholine.[4] In the future, there may be drugs that take advantage of the differing pharmacological sensitivities of the mature and immature receptors

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Editor—Indeed, the adult form of AchR has the αε instead of the αγ receptive site. However, the differences between the adult and fetal receptors are not known to qualitatively affect the structure activity relationships and the conformation activity relationships of the neuromuscular blocking agents discussed. For simplicity, I therefore used the generic nomenclature in the review, except that '(or ε)' was inserted when αγαδβ was first mentioned. The dimensions of the AchR were also generic. Different preference of neuromuscular blocking agents for either the αγ (or αε) or the αδ receptive site[1] was also left out.

Being mindful of the need for greater precision, I have updated the topology of the receptive sites and fitted molecules of Ach into the picture with what appears to be the correct dimensions and orientation, as follows.

If 20 Å separates the receptive sites and each of the two Ach molecules that open the ionic channel occupies 6 Å with its methonium head, 8 Å remains in the lumen for the influx of the cations. This is just enough to prevent a bottleneck at the level of the receptive sites, considering that the trans-membrane tube portion of the channel also measures about 8 Å.[2] Relative to the depolarizing cations and the channel, Ach is a large molecule.

Each subunit has a positive and a negative face, arranged so that the positive face of each subunit faces the negative face of its neighbour (Fig. 1). It is the negative face of the γ (or ε) subunit that faces the α subunit and attracts the positively charged methonium head of Ach to their interface.[3] For Ach to be bound to the α subunit, and if its methonium head fits the inferface, its acetyl portion has to point to the α subunit, not the other way around. Looking from the synaptic cleft down the receptor channel, this means that Ach sits clockwise from the carbonyl O to the quaternary N. This is because the subunits are clockwise from the α to the γ (or ε).[3]

Scientists may one day taylor the relaxant molecule to fit the specific receptive site, however, specific targeting of neuromuscular blocking agents to the adult or fetal type AchR seems a remote challenge.

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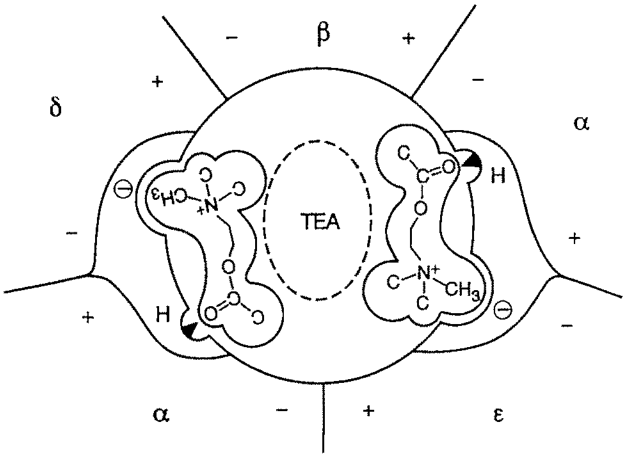

Fig 1 Topology of the AchR at the receptive sites viewed from the synaptic (extracellular) side One receptive site consists of the α and the ε (or γ) subunits, the other of the α and the δ subunits Each site has an anionic center for the methonium head of Ach and a hydrogen bond donor (H) for the carbonyl O atom Tetraethylammonium (TEA) is the largest cation to pass between the receptive sites and the transmembrane portion of the open channel. The subunits are oriented after Prince and Sine,[3] and the proportions are after Lee[2]

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The alveolar lining

Editor—In their recent editorial, Dorrington and Young[1] are to be commended for daring to question the culturally embedded concept that there is a continuous liquid (bubble) lining to the normal alveolus—a sacred cow of respirologists and neonatologists long challenged by this 'dissident'.[2 3] Those authors together with Bangham[4] in his letter, and even the original proponents[5] of the 'bubble' model all point out that, for a series of interconnected bubbles to be stable, it is vital that there be no surface communication between them Otherwise, surfactant monolayers could spread and equalize surface tension. Even if the surfaces are not connected *via* terminal bronchioles, they are surely connected *via* the abundant pores of Kohn which are large enough to allow direct passage of a macrophage from an alveolus to its immediate neighbours.[3] In response to such criticisms, 'the believers'[6] have frozen lungs and claim to have demonstrated a liquid lining, but only after artefactually exsanguinating those lungs, thus removing micro-concavities caused by red cells bulging their way through capillaries underlying the very thin alveolar wall. Classical studies of non-exsanguinated frozen lungs display convex areas of alveolar epithelium apparently free of fluid, as reviewed.[1]

Dorrington and Young must be challenged, however, when they boldly state that there are 'two fundamental errors' in my review.[7] First, my discussion of the role of surfactant in alveolar fluid balance is hardly a 'fundamental error' if the normal homeostatic mechanisms are not mentioned until the next paragraph, when ion-channel pumps are described—but admittedly described as 'water pumps' rather than 'aquaporins'. However, this is an interesting point which they raise because, when adsorbed, surface-active phospholipid (SAPL) can impart semi-permeability which is vital before ion gradients can be maintained long enough to shift water.[8]

Second, they are correct in stating that, to physicists, a non-spherical continuous liquid lining is inconceivable, but the areas over which asperities on the epithelial surface would breach that liquid lining would be negligible unless there were some degree of hydrophobicity of the alveolar wall A hydrophilic lining would cause a meniscus of fluid to encroach until only a point or ridge of tissue were exposed to air, just as water rises up a hydrophilic glass plate to a height of many alveolar diameters, even when immersed vertically. It is a moot point as to how much of the alveolar surface needs to be fluid-free before the instability of interconnected bubbles no longer applies An interesting example of the principle of dewatering surfaces by bound (adsorbed) surfactant[3] occurs on the ocular surface where adsorbed SAPL ruptures the tear film unless we blink every 20 s or so [9] This time-dependent aspect of wetting/dewetting must cast doubt upon our use of static models, especially when 'bulging' caused by red cells means that areas on the alveolar surface are 'oilcanning' at frequencies approaching that of the electric mains, *viz.* 50 Hz.[10] At the microscopic level, the system is highly dynamic.

Dorrington and Young have taken a major step in expressing so clearly the shortcomings of the concept of a continuous liquid lining to the alveolus which I challenged 20 yr ago.[2] When are they going to address the next sacred cow that surfactant acts only at a liquid–air interface in the lung? It has been a century since surfactants were first studied at solid surfaces in the physical sciences and discussion of the physiological implications has been welcomed in relation to many organs except the lung.[3] Maybe the 'black films' to which Dorrington and Young refer are the adsorbed oligolamellar linings of SAPL demonstrated in the alveolus by Ueda and colleagues[11] and ourselves.[3,8]

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Editor—We thank Professor Hills for his constructive comments about our editorial.[1] He calls us to account for our claim that he has made 'two fundamental errors' in his otherwise challenging critique of the established dogma that the pulmonary alveoli are lined in health with a continuous layer of liquid.

One of the points we made in our editorial was that Hills claims that passive forces alone account for the absorption of liquid from the corners of alveoli. This was the view he propounded using a diagram in his review published in this journal in 1990,[2] and elsewhere, where it was hypothesized that liquid is induced by the hydrophobicity of the alveolar epithelium to sit in globules that present a convex surface to gas in the alveoli. The hydrostatic pressure within these globules would be higher than atmospheric pressure, to balance forces at the liquid–gas interface, and would act to encourage liquid to move from the globule into the pulmonary interstitium. A virtually identical diagram is used in the review by Hills to which we referred, published in 1999 [3] In the legend to this diagram (Fig. 8), Hills writes that the surface tension in globules will 'assist physiological water pumps' in resolving oedema The nearby text qualifies the term 'physiological water pumps' with the parenthetic expression 'protein-oncotic and ion channel'.

We concede that these terms can be taken to refer to the process of active sodium transpost from the alveoli, as elucidated by Basset and colleagues,[4] and Matthay and colleagues.[5] However, the terminology used by Hills, in both his review[3] and his recent correspondence to which this letter is a reply, is unconventional. The term 'pump' is usually reserved in membrane physiology to refer to primary active transporters that utilize adenosine triphosphate (ATP) to move a molecule across a cell membrane against its electrochemical gradient. No pump, in this sense, has yet been found for water. The term 'ion channel' is usually reserved for a membrane channel that is to some extent selectively permeable to an ion that moves through the channel down its electrochemical gradient The term 'aquaporin' designates a transmembrane channel that is at least partially selective for water. The component of water uptake from the alveoli associated with the utilization of ATP has been shown to require the sodium-potassium pump on the basolateral membrane of epithelial cells, sodium channels on the apical membrane of the cell, and, in some species at least, a sodium-glucose co-transporter, also on the apical membrane.[4,5] The role of aquaporins in this process remains unclear.[6]

The other point made in our editorial that Hills appears to challenge is our claim that he relies upon the concept of a hydrophobic alveolar surface to account for why small amounts of liquid collect into pools or globules on the alveolar surface, rather than forming a thin film wetting the whole surface. Our claim appears to be confirmed by a statement in the same legend referred to above (reference 2, Fig. 8): 'surfactant absorbs to . . . tissue surfaces, rendering tissue less wettable to explain the apparently fluid-free areas'. We set out to show in our editorial that, even if the alveolar surface were highly hydrophilic, liquid on the alveolar surface would cease to form a continuous coating of the surface when the volume of liquid in the alveolus was no longer sufficient to permit immersion of the whole alveolar surface below a spherical gas-liquid surface. The micrographs of Bachofen and colleagues illustrate this phenomenon.[7] We believe that this statement addresses Hills' comment in his letter that 'it is a moot point as to how much of the alveolar surface needs to be fluid-free before the instability of interconnected bubbles no longer applies'. We have described the limiting case of the minimum volume of liquid that could be sustained as a continuous lining by a highly hydrophilic surface. It appears likely that a less hydrophilic surface would lead to fragmentation of alveolar liquid at a larger volume of liquid, and that a highly hydrophobic surface might be able to maintain a substantial proportion of its area free of liquid, even when a large volume of liquid is in the alveolus. The extent to which the alveolar surface may be regarded as either hydrophilic or hydrophobic appears to us to be unknown.

K. L. Dorrington
J. D. Young
Oxford
UK

1 Dorrington KL, Young JD. Development of the concept of a liquid pulmonary alveolar lining layer. *Br J Anaesth* 2001; **86**: 614–17
2 Hills BA The role of lung surfactant. *Br J Anaesth* 1990; **65**· 13–29
3 Hills BA An alternative view of the role(s) of surfactant and the alveolar model. *J Appl Physiol* 1999; **87** 1567–83
4 Basset G, Crone C, Saumon G. Fluid absorption by rat lung *in situ* pathways for sodium entry in the luminal membrance of alveolar epithelium. *J Physiol* 1987; **384**: 325–45
5 Matthay, MA, Flori HR, Conner ER, Ware LB. Alveolar epithelial fluid transport· basic mechanisms and clinical relevance. *Proc Assoc Am Physicians* 1998; **110**: 496–505
6 Song Y, Fukuda N, Bai C, Ma T, Matthay MA, Verkman AS Role of aquaporins in alveolar fluid clearance in neonatal and adult lung, and in oedema formation following acute lung injury: studies in transgenic aquaporin null mice. *J Physiol* 2000; **525**: 771–9
7 Bachofen H, Schurch S, Michel RP, Weibel ER. Experimental hydrostatic pulmonary edema in rabbit lungs. *Am Rev Respir Dis* 1993; **147**: 989–96

Transtracheal high frequency jet ventilation for endolaryngeal surgery

Editor—Bourgain and colleagues[1] are to be congratulated on their excellent study of transtracheal high frequency jet ventilation for endolaryngeal surgery The work helps to dispel the myths that the technique is difficult and dangerous. As with previous smaller studies, it is easily performed and taught, and provided it is carried out with care, it is also safe. The authors do not mention the duration of the procedures, but we have found that normocapnia can be maintained for at least 57 min, and probably indefinitely.[2]

We have to disagree with the comment that conventional i.v. catheters are not safe, however. We have been using 16g Abbocath (Abbot, Sligo, Ireland) i.v. cannulas routinely for many years and published a series of 90 consecutive patients.[2] With experience, the cannulas rarely kink, and the attachment of a T-piece connector (Abbott, Ireland, Sligo) to the cannula makes kinking by repeated engagement/disengagement to the jet ventilator less likely. In the event of serious kinking, it is relatively simple to replace the cannula over a wire.

One advantage of these catheters is that they are readily available in all sites, and we have successfully placed them in emergency situations outside of the ENT theatres.

W C. Russell
J. M C. Greiff
Leicester
UK

1 Bourgain JL, Desruennes E, Fisher M, Ravussin P. Transtracheal high frequency jet ventilation for endoscopic airway surgery: a multicentre study. *Br J Anaesth* 2001; **87**: 870–5
2 Russell WC, Jones GW, Maguire AM. Cricothyroidotomy and transtracheal high-frequency jet ventilation for elective laryngeal surgery. An audit of 90 cases. *Anaesth Intens Care* 2000, **28**: 62–7

Editor—We thank Russell and Greiff for their comments on our study on transtracheal high frequency jet ventilation for endoscopic airway surgery.[1]

When we started work in this area (15 yr ago), we compared different injection devices. We abandoned Tuohy needles after a case of extensive postoperative subcutaneous emphysema, related to an injury to the trachea from the needle during an episode of coughing. Using the Surflo IV catheter 14 gauge (Terumo, Belgium), we occasionally observed serious kinking resulting in difficulty with cannula replacement over a wire.

We agree that an i.v. catheter may be useful in emergency situations because they are available everywhere. As we did not find any injection problems with them in our study, we recommend the use of intra-arterial or Ravussin catheters in scheduled airway surgery.

J -L Bourgain
E. Desruennes
Villejuif
France

1 Bourgain JL, Desruennes E, Fisher M, Ravussin P Transtracheal high frequency jet ventilation for endoscopic airway surgery. a multicentre study. *Br J Anaesth* 2001, **87**: 870–5

Avoiding airway obstruction

Editor—I read with interest the case report by Kurian and colleagues[1] about an obstructed catheter mount As stated, this has occurred previously.[2]

I disagree with their statement: 'The equipment check even if it had been performed with the offending item in circuit would not have identified the obstruction' The whole purpose of performing an equipment check is to be 100% certain that one can ventilate the patient's lungs with 100% oxygen by a face mask. To do this, the breathing system being used must be checked *in its entirety* before the patient is anaesthetized. In our institution, the catheter mount, HME and face mask are connected to the breathing system from the start, and the patency of the system is checked by placing the face mask against one's hand, creating an airtight seal, while squeezing the bag (with the oxygen flowmeter turned on) This manoeuvre, together with the use of an oxygen analyser, ensures that 100% oxygen can be administered under positive pressure *via* the mask.

When an LMA[†] tube is connected to the system, no other new items are inserted into the breathing system, thus simplifying the diagnostic pathway described by Kurian and colleagues[1], should an obstruction occur I suggest that, had they followed this procedure during their preoperative check, the incident could have been avoided.

D. Mayne
Gateshead
UK

1 Kurian J, Renwick N. An unusual case of airway obstruction. *Br J Anaesth* 2001; **87**· 804–5
2 Thomas R, Finch S. A blocked catheter mount. *Anaesthesia* 2001; **56**. 88

Editor—Thank you for the opportunity to respond to Dr Mayne's letter. The other similar case report occurred almost on the same day as ours, and one of the reasons for submission of our letter was the continued occurrence of similar incidents with disastrous outcomes

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[†] LMA® is the property of Intavent Limited

We still stand by our statement to which Dr Mayne has taken objection. The manoeuvre which he has described, otherwise known as the 'pressure leak test', is mainly aimed at looking for leaks in the system and still would have missed a block in the catheter mount. The bag will inflate with the pressure-limiting valve turned shut, and deflate with opening of the valve, whether the patient end is occluded or not This hypothesis was tested on 20 experienced anaesthetists in a single blinded fashion, and none could detect the obstruction, except those who routinely felt for the gas flow.

We would not be as bold as Dr Mayne and expect 100% certainly from any equipment check. This kind of thought process, we believe, will hinder early identification and correction of potentially life-threatening equipment malfunction.

J Kurian
M Renvick
Carshalton, Surrey
UK

Delayed diagnosis of cardiac tamponade

Editor—Dunsire and colleagues' paper on delayed diagnosis of cardiac tamponade makes interesting reading,[1] and deserves further comment.

The decision to proceed to emergency laparotomy in the first instance seems sensible, given the lack of imaging facilities at the receiving hospital. In the presence of congested hepatic veins and an engorged inferior vena cava, cardiac tamponade should have been seriously considered at that point. Furthermore, the lack of free blood in the abdomen should have alerted the surgeon to other causes of hypotension. The simple procedure of creating a subxiphoid pericardial window would have excluded a tamponade quickly and definitively, and is straightforward to perform at laparotomy.

The finding of blood on opening the pericardium should prompt extension of the incision into a median sternotomy, to allow inspection of the heart and repair of damaged structures. If the surgeon was not happy to proceed to sternotomy, the placement of a pericardial drain would likely have had a similar outcome to that described. Given the lack of a definitive diagnosis at laparotomy, the decision to return the patient to a non-intensive care setting, despite continuing haemodynamic instability, could also be called into question.

We agree that the lack of a chest radiograph hindered initial assessment. This is contrary to established advanced trauma life support principles. The finding of a fluid level in the hemithorax on an erect chest radiograph is diagnostic of haemothorax in the context of trauma, and should lead to prompt insertion of a chest drain. It is well known that the chest radiograph can be normal in acute cardiac tamponade, but the identification of a haemothorax before laparotomy would heighten suspicions of significant intrathoracic injury on discovering the lack of intra-abdominal haemorrhage.

Catheter drainage of the pericardium has been reported in the context of penetrating trauma.[2] We would re-emphasize the need for very close supervision by specialist cardiothoracic surgeons with immediate access to the operating room if patients are to be treated in this way.

We would argue that pigtail catheter drainage is the initial treatment of choice for pericardial effusions and cardiac tamponade in the non-traumatic scenario; trauma patients who are suspected of cardiac tamponade require urgent evaluation by echocardiography (transthoracic or transoesophageal), or by creation of a subxiphoid pericardial window in the operating room.

We agree with Dunsire's conclusion that cardiac tamponade must be high on the index of suspicion if the diagnosis is not to be delayed or missed.

C. A. Graham
G M. Wares
Glasgow
UK

1 Dunsire MF, Field J, Valentine S. Delayed diagnosis of cardiac tamponade following isolated blunt abdominal trauma *Br J Anaesth* 2001; **87**: 309–12

2 Graham CA, Latif Z, Munithi EW, Belcher PR, Ireland AJ. Acute traumatic cardiac tamponade treated solely by percutaneous pericardial drainage *Injury* 1998, **29**: 473–4

Editor—I thank Graham and Wares for their interest in my paper.[1] I agree with their opening comments that a laparotomy was indicated given the lack of imaging A lack of free blood in the peritoneal cavity combined with engorged hepatic veins and inferior vena cava should have alerted the surgeon to the possibility of cardiac tamponade. I would contend that the anaesthetist also should have been alert to other causes of hypotension. Had a central line been inserted at this stage, the finding of a high central venous pressure combined with hypotension would have indicated a cardiac problem and prompted further exploration. Creation of a subxiphoid pericardial window would have been appropriate, had the diagnosis of cardiac tamponade been considered at the time of surgery. After negative laparotomy, with ongoing haemodynamic instability, I agree that it would also have been appropriate to transfer the patient to an intensive care unit with imaging facilities.

The lack of a chest radiograph is contrary to established advanced trauma life support principles, and both surgeon and anaesthetist should have insisted on one being performed preoperatively. Had one been performed and a haemothorax noted, this would have indicated potentially serious intrathoracic injuries. However, given the mechanism of injury, lack of other imaging, and the clinical picture, there was still a high risk of serious intra-abdominal injury. The decision to proceed to laparotomy would have been correct, even in the presence of a documented haemothorax.

I note the comments concerning catheter drainage of the pericardium in penetrating trauma,[2] and agree that if it is to be managed conservatively, cardiac surgeons and operating theatre space must be readily available. This is not standard treatment, as the vast majority of penetrating cardiac injuries require surgical intervention, whereas there is literature to support echocardiography and catheter drainage of pericardial tamponade[3 4] in the non-traumatic scenario.

M Dunsire
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1 Dunsire MF, Field J, Valentine S. Delayed diagnosis of cardiac tamponade following isolated blunt abdominal trauma. *Br J Anaesth* 2001; **87**: 309–12

2 Graham CA, Latif Z, Munithi EW, Belcher PR, Ireland AJ Acute traumatic cardiac tamponade treated solely by percutaneous pericardial drainage. *Injury* 1998; **29**: 473–4

3 Salem K, Mulji A, Lonn E. Echocardiographically guided pericardiocentesis: The gold standard for the management of pericardial effusion and cardiac tamponade. *Can J Cardiol* 1999; **15**: 1251–5

4 Tsang TS, Oh JK, Seward JB. Diagnosis and management of cardiac tamponade in the era of echocardiography. *Clin Cardiol* 1999; **22**: 446–52

Unnecessary Caesarean section due to silent CTG

Editor—We read with interest the case report by Immer-Bansi and colleagues,[1] describing an unnecessary emergency Caesarean section following an emergency thrombectomy. The need for Caesarean section arose due to loss of beat-to-beat variability on the cardiotocograph (CTG) whilst the 30-week primigravida was under general anaesthesia. We commend the authors on instituting continuous fetal monitoring during surgery. Their conclusion that loss of beat-to-beat variability resulted from the effects of general anaesthesia alone is valid. But, the same CTG findings are seen during fetal sleep.[2]

There is no mention of whether left lateral tilt was employed during thrombectomy in this patient. We accept that there was no apparent aortocaval compression; and covert aortocaval compression is unlikely during general anaesthesia because of attenuation of baroreceptor reflexes. However, left lateral tilt of 15° has been recommended as a means of reducing aortocaval compression in women undergoing Caesarean section,[3] and its use is commonly accepted for women undergoing non-obstetric surgery in the third trimester.

Despite this, the benefits of left lateral tilt for Caesarean section have been disputed in a randomized controlled trial[4] where umbilical artery Po_2 was significantly lower in the tilted group compared to the supine group. We are interested in whether the authors routinely use left lateral tilt when anaesthetizing women in their third trimester.

H. Hartley
J. Stone
Guildford
UK

1 Immer-Bansi A, Immer FF, Henle S, Sporri S, Petersen-Felix S. Unnecessary emergency Caesarean section due to silent CTG during anaesthesia? *Br J Anaesth* 2001; **87**: 791–3

2 Sampson MB, Mudaliar NA, Lele AS Fetal heart rate variability as an indicator of fetal status. *Postgrad Med* 1980; **67**: 207–10, 213–5

3 Crawford JS. *Principles and practice of obstetric anaesthesia.* 5th Edn. Oxford. Blackwell Scientific, 1984: 286–7

4 Matorras R, Tacuri C, Nieto A, Gutierrez de Teran G, Cortes J. Lack of benefits of left tilt in emergent cesarean sections: a randomized study of cardiotocography, cord acid-base status and other parameters of the mother and the fetus. *J Perinatal Med* 1998; **26**: 284–92

Editor—Thank you for the opportunity to respond to the letter of Hartley and Stone, and for their interest in our case report. We agree that reduced beat-to-beat variability can also be seen during fetal sleep, and normal variability will return if the fetus is aroused by external stimulation. This was not clearly stated in our case report; however, a wake-up attempt was performed as can be seen in the Figure.

Concerning left lateral tilt, we routinely use a wedge under the right hip from the 20th week until term. This was also employed in the presented case. A left lateral tilt is recommended in the latest textbooks on obstetric anaesthesia although the hard evidence for using this manoeuvre is limited. We are aware of the paper by Matorras and co-workers (their reference 4), but those workers had a very high percentage of Caesarean sections performed under general anaesthesia (86%). More than 80% of our Caesarean sections are performed under regional anaesthesia. Latent aortocaval compression may become manifest during regional anaesthesia because sympathetic compensatory mechanisms will be attenuated or totally blocked.

A. Immer-Bansi
S. Petersen-Felix
Bern
Switzerland

Intrathecal ropivacaine or bupivacaine with fentanyl for labour

Editor—Hughes and colleagues[1] have presented an interesting study comparing intrathecal ropivacaine or bupivacaine with fentanyl for labour. To our knowledgement, this is the first study to have compared intrathecal ropivacaine/fentanyl with the standard bupivacaine/fentanyl mixture, which is the most commonly used combination for the intrathecal component of a combined spinal-epidural (CSE) in patients in labour in the UK.

We would suggest that the first step in assessing the value of ropivacaine as an intrathecal drug would be to assess its relative potency in comparison with bupivacaine. Previous work has demonstrated the lower poteny of ropivacaine in the epidural space, and this might also be expected to apply when the drugs are administered intrathecally.[2 3] It is, therefore, no surprise to find less motor block with ropivacaine than bupivacaine in this study. Interestingly, severe motor block, the main concern for safe maternal ambulation, was not found in either group.

It is also not a surprise to find no difference in analgesic efficacy between the two mixtures, despite the lower potency of ropivacaine. In early labour, fentanyl alone can produce near complete analgesia,[4] so both mixtures probably exceed the minimum effective dose. Indeed, our view is that a CSE is most strongly indicated for the distressed woman in advanced labour. Unfortunately, this study does not tell us how the two mixtures will perform in this more relevant clinical situation.

Given these criticisms, we are grateful to Hughes and colleagues for this first assessment of ropivacaine in this role. An epidural study has shown a longer duration of action of ropivacaine than bupivacaine in this space.[5] If an equipotent dose of intrathecal ropivacaine prolongs the duration of the spinal component of a CSE, this would be a most useful feature of the drug. Perhaps the authors would consider this as their next study.

A J Pinder
M Dresner
Leeds
UK

1 Hughes D, Hill D, Fee JPH Intrathecal ropivacaine or bupivacaine with fentanyl for labour. *Br J Anaesth* 2001, **87**. 733–7

2 Polley LS, Columb MO, Naughton NN, Wagner DS, van de Ven CJ. Relative analgesic potencies of ropivacaine and bupivacaine for epidural analgesia in labour: implications for therapeutic indices. *Anesthesiology* 1999, **90**. 944–50

3 Capogna G, Celleno D, Fusco P, Lyons G, Columb M Relative potencies of bupivacaine and ropivacaine for analgesia in labour. *Br J Anaesth* 1999; **82**: 371–3

4 Kelly MC, Carabine UA, McKinney KA, Mirakhur RK Fentanyl, bupivacaine or fentanyl and bupivacaine for intrathecal analgesia in labour. *Int J Obstet Anesth* 1997; **6**. 204–5

5 Parpaglioni R, Capogna G, Celleno P. A comparison between low dose ropivacaine and bupivacaine at equianalgesic concentrations for epidural analgesia during the first stage of labour. *Int J Obstet Anesth* 2000; **9**: 83–6

Editor—Thank you for the opportunity to reply to Pinder and Dresner. They have raised many valuable points for discussion. As they correctly point out, research has shown ropivacaine to be less potent than bupivacaine when administrated *via* the epidural route.[1] This may also apply to intrathecal use, but as ours was the first comparative study in the UK of intrathecal ropivacaine and bupivacaine for labour analgesia, we felt it appropriate to start with a study employing equal doses of both local anaesthetics. If intrathecal ropivacaine is to have any place in clinical practice, it must compare favourably with the current bupivacaine regime used in most units, and this was the basis of our study.

The comments regarding motor blockade and safe ambulation are open to dispute. Women with even moderate motor weakness would, we suggest, be unlikely to mobilize safely unaided. The ability to walk independently and safely is perhaps the end-point we should concentrate on. In this respect, it has now been established that the absence of motor weakness is the major factor determining safe and normal ambulation[2] In this respect, the women receiving intrathecal ropivacaine were at a distinct advantage.

Intrathecal opioid alone can produce adequate analgesia for early labour. We have published work in this area demonstrating effective analgesia with intrathecal alfentanil.[3] Although CSE analgesia may be particularly advantageous for women in advanced labour, it is difficult ethically and practically, to limit a CSE study such as ours to women in this category. Only with increased use of intrathecal ropivacaine, will sufficient experience be gained to assess performance in this group of women. Of note, a number of women in our study had effective analgesia with intrathecal ropivacaine at cervical dilatation of 5 or 6 cm.

Following on from this study, we have embarked on further research investigating varying doses of intrathecal ropivacaine and bupivacaine, again comparing efficacy, motor block and duration. This will hopefully enable us to address the outstanding issues raised.

D. A. Hughes
D A. Hill
J P H Fee
Belfast
UK

1 Capogna G, Celleno D, Fusco P, Lyons G, Columb M. Relative potencies of bupivacaine and ropivacaine for analgesia in labour. *Br J Anaesth* 1999; **82**: 371–3

2 Hughes DA, Hill DA. Intrathecal alfentanil with and without bupivacaine for analgesia in labour *Anaesthesia* 2000, **55**: 1116–21

3 Pickering AE, Parry MG, Ousta B, Fernando R Effect of combined spinal-epidural ambulatory labor analgesia on balance. *Anesthesiology* 1999; **91**: 436–41

Combined epidural and general anaesthesia in a patient with a transplanted heart undergoing upper abdominal surgery

Editor—An early case report[1] described a body surface operation under general anaesthesia in a patient with a transplanted heart. Though epidural anaesthesia was considered inappropriate for that particular operation, hypotension and infection in the central nervous system were cited as potential risk factors mitigating against its use. Sixteen years on, the combined use of general anaesthesia with epidural blockade, particularly in upper abdominal surgery, has become widely accepted as a means of achieving total postoperative pain control with less pulmonary morbidity, and other beneficial features lead to a swifter and smoother return to normal function.

We report a 47-yr-old male patient with a transplanted heart who had an 8 cm cyst in the tail of the pancreas secondary to steroid-induced pancreatitis. Splenectomy and resection of the distal pancreas was the definitive surgical cure but preservation of the spleen was considered essential in an immunocompromized patient; a Roux-en-y-cyst-jejunostomy was the preferred surgical option.

A transplanted heart has its own SA node as a pacemaker, though the recipient's atrial remnant may still contain its own genetic SA node. This can give rise to two 'p' waves on the ECG. There is no normal anatomical continuity between the transplanted heart and the recipient's autonomic nervous system. As a result, the cardiac component of the fight or flight response is delayed being dependent on direct action on myocardial cells of circulating catecholamines deriving from the adrenal medulla. The pressor response to stimuli (such as laryngoscopy) is delayed. Though the transplanted heart is often described as denervated, it is an inaccurate term because the transplant retains its own electrical conducting system but is devoid of functional autonomic innervation There is some evidence that slow development of cardiac re-innervation may occur.[2] The autonomic supply to the peripheral vasculature is, of course, preserved. The transplanted heart is unable to participate in the baroreceptor reflex and there is no chronotropic response to carotid massage or fluctuations in arterial pressure. There is, therefore, no reflex tachycardia in response to hypovolaemia or hypotension, and the importance of maintaining an adequate circulating preload to maintain stroke volume has been described.[3] Also, it has been asserted that a transplanted heart tolerates hypertension better than hypotension.[4]

Pharamacological responses are altered, drugs acting on the autonomic nervous system do not modulate the transplanted heart. Atropine does not produce a chronotropic effect and it has been suggested that the effect of neostigmine (if used) may not need to be modified with a vagolytic, although this is contentious.[5] The accepted treatment for acute bradycardia in these patients is a direct-acting B_1 agonist such as isoprenaline

The article by Lyons and colleagues[6] lists a number of potential non-cardiac surgical problems to which transplant patients may be prone, such as complications related to the transplant operation itself, complications of immunosuppressive and/or steroid therapy, extension of primary disease (atherosclerosis), and complications associated with anticoagulant therapy, if this is part of long term-therapy Though subarachnoid anaesthesia has been described in these patients,[3] we decided to use epidural combined with general anaesthesia, titrating local anaesthetic dosage to cardiovascular response in the usual way. Our patient was not on anticoagulant therapy.

The patient's history included heart transplant 3 yr previously for cardiomyopathy and subsequent chronic renal impairment and hypertension, the renal dysfunction was secondary to long-term immunosuppressive therapy The main symptoms from the pancreatic cyst were abdominal pain and nausea. Exercise tolerance was one flight of stairs, which would induce breathlessness and fatigue. Resting arterial pressure was 160/90 mm Hg and heart rate 90 min^{-1}, with no signs of heart failure. A routine cardiac biopsy 1 month previously had excluded evidence of graft rejection. Preoperative haemoglobin was 8.9 g dl^{-1}, unchanged from previous testing and low because of chronic renal impairment.

In a sterile manner, we sited a T9/10 epidural catheter under light sedation (midazolam and diamorphine), as well as peripheral venous access and a radial artery cannula for invasive pressure monitoring. Induction of anaesthesia was with propofol, followed by atracurium and tracheal intubation. Anaesthetic maintenance was with sevoflurane in oxygen and nitrous oxide A left internal jugular catheter was inserted (taking sterile precautions), avoiding the right side which was scarred from multiple previous procedures including regular cardiac biopsies. Antibiotic cover was with co-amoxyclav.

Before the start of surgery, we injected a loading dose of diamorphine 3 mg through the epidural catheter followed by 2 ml increments of 0.75% bupivacaine to a total of 8 ml. An infusion (8 ml h^{-1}) was then started using 0 1% bupivacaine with diamorphine 25 $\mu g\ ml^{-1}$. One litre each of normal saline and gelofusin were infused as a preload to maintain the CVP at 12–15 mm Hg. Reduction of arterial pressure following the epidural loading dose was corrected with increments of ephedrine (total 20 mg) followed by methoxamine (total 8 mg), to maintain a mean arterial pressure greater than 80 mm Hg. At this point, we decided to infuse norepinephrine continuously at a rate of 5–8 $\mu g\ kg^{-1}\ min^{-1}$.

The operation was successful and the patient was discharged from the operating theatre to high dependency care for continued invasive monitoring and epidural infusion over the subsequent 4 days The norepinephrine infusion was only required for 2 h postoperatively, after which it was discontinued and arterial pressure gradually returned to its former hypertensive level.

In summary, we used an epidural infusion effectively in a patient with a transplanted heart undergoing upper abdominal surgery The risks of infection from invasive monitoring as well as those associated with extradural anaesthesia on the transplanted heart in an immunocompromized patient were considered and the decision was made to proceed. We agree with Shaw and colleagues,[7] who described a patient who received epidural anaesthesia for postoperative pain control, and implied that the technique was justifiable The outcome for our patient was favourable.

K Grimsehl
I. D Levack
Dundee
UK

1 Bricker SRW, Sugden JC Anaesthesia for surgery in a patient with a transplanted heart. *Br J Anaesth* 1985, **57**. 634–7
2 Wilson RF, Christensen BV, Olivari MT, Simon A, White CW, Laxson DD Evidence for structural sympathetic reinnervation after orthotopic cardiac transplantation in humans *Circulation* 1991; **83**: 1210–20
3 Cheng DCH, Ong DD Anaesthesia for non-cardiac surgery in heart-transplanted patients *Can J Anaesth* 1993; **40**. 981–6
4 Tsarikis AG, Donald DE, Rutishauer WJ. Cardiovascular responses to hypertension and hypotension in dogs with denervated hearts *J Appl Physiol* 1969; **27**: 817–21
5 Backman SB, Ralley FE, Fox GS Anaesthesia for cardiac transplant patients. *Can J Anaesth* 1994, **41**. 655–6
6 Lyons JB Chambers FA, MacSullivan R, Moriarty DC Anaesthesia for non-cardiac surgery in post-cardiac transplant patients. *Irish J Med Sci* 1995; **164**. 132–5
7 Shaw IH, Kirk AJB, Conacher ID. Anaesthesia for patients with transplanted hearts and lungs undergoing non-cardiac surgery. *Br J Anaesth* 1991, **67**. 772–8

Editor—Thank you for the opportunity of responding to the letter by Grimsehl and Levack We anaesthetized the man who was the subject of the 'early case report' in 1983,[1] at which time he was one of perhaps fewer than 10 cardiac transplant survivors in the UK. Certainly this was the information that our patient gave us, and I break no confidences in revealing that he insisted on general anaesthesia for his relatively minor surgery (avulsion of all toe nails because of fungal infection), in order to persuade clinicians in this country that the technique was safe His motive was specific· he wanted to pave the way for one of his fellow recipients, a popular individual who received considerable press attention at the time, to undergo general anaesthesia for total knee-replacement.

Worldwide, there were said to be over 130 surviving recipients in 1980,[2] at least some of whom subsequently had undergone major non-cardiac sugery,[3] but in the UK there was minimal experience of such cases, and this mainly was the reason for our somewhat timorous approach. The combination of thiopental, nitrous oxide, oxygen and halothane is hardly adventurous, but it had the benefit of familiarity and was more than sufficient for the trivial surgery which did not warrant epidural analgesia The management of hypotension associated with this technique certainly would not trouble many contemporary anaesthetists, particularly now that there is much wider experience of such patients. Indeed, the theoretical possibility of hypotension did not trouble us in 1983 nearly as much as concerns about the risks of central neuraxial infection in an immunocompromized subject This hazard remains, but risk-benefit analysis clearly favours the use of epidural analgesia in a case such as the one described above. I suspect, however, that we might still not have been so bold in the early 1980s: anecdotal information has it that our patient's fellow recipient did recieve his total knee replacement—under general anaesthesia.

S R W Bricker
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Anaesthesia for cataract surgery

Editor—I would like to make three points on the interesting article by Allman and colleagues [1] The authors state that peribulbar block is the anaesthetic technique of choice for cataract surgery They refer to work published in 1996 Maybe peribulbar block was the technique of choice in 1996, but now lens emulsification is more commonly performed under topical anaesthesia.[2–4] Anaesthetic drops are sufficient to control the discomfort as phacoemulsification of the lens is not painful. Consequently, it is inappropriate to compare the efficacy of two anaesthetic drugs in such procedures. It would be better to do such a study during posterior segment surgery, which is more painful. In addtion, their patients were given alfentanil and midazolam. With this combination of drugs, it is not easy to assess pain.

We try to use purified anaesthetic drugs which do not contain preservative and which are not extracted from animals, during these procedures. Articaine contains metasulfite which may produce allergic reactions [5 6] We would accept replacing the mixture we usually use (lidocaine and bupivacaine), if any new local anaesthetic drug to become available was purified

In the discussion, the authors reported three cases of optic atrophy after the use of prilocaine with felypressin, and they have now stopped using prilocaine. Unfortunately, the references of these three cases are missing Felypressin is as effective a vasoconstrictor as epinephrine [7] We think that these complications are probably due to felypressin and not to prilocaine

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Editor—Many thanks for the opportunity to comment on Dr Calenda's letter. Although the use of topical anaesthesia for cataract surgery is certainly increasing, in our institution this still accounts for less than 5% of all cases. The main advantage of peribulbar block remains the degree of akinesia obtained and this (rather than analgesia) was our main outcome measure.

We used articaine with epinephrine (1 in 200 000) as we were initially uncertain if a plain solution would give sufficient duration of block for surgical extraction—it is not recommended for dental use. Metabisulphite is widely used in standard preparations of local anaesthetic containing epinephrine with few problems. However, it may be preferable to use local anaesthetic solution without either additive, if possible. We are currently undertaking a study using plain articaine with a sub-Tenon technique and the duration of action does appear to be sufficient for cataract extraction (unpublished data).

Widespread use of prilocaine 3% with felypressin for eye surgery was curtailed in January 2000 when the manufacturers (Astra Zeneca) issued a hazard notice describing three cases of optic atrophy. The precise cause remains unclear but prilocaine, the vasopressor and the technique could all be potentially implicated. As prilocaine 3% remains unlicensed for peribulbar use, it would seem imprudent to continue using it following such notification.

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Use of remifentanil in fast atrial fibrillation

Editor—We read the report by Kurdi and colleagues[1] with interest. We would like to report a case of the use of remifentanil to slow the heart rate with benficial effects for the patient. A 90-yr-old female, weight 54 kg, presented acutely with a painful pelvic mass. She had a past medical history of stable angina and hypothyroidism. Her medications included thyroxine 500 µg OD, frusemide 40 mg OD, and glyceryl trinitrate spray 300 µg PRN. On examination, she was noted to have atrial fibrillation with a rate of 115 beats min^{-1}. Surgery was delayed to facilitate oral loading with digoxin, and to allow an ultrasound examination which confirmed the presence of a mass arising from the uterus. Following 3 days of digoxin therapy, the patient's heart rate had fallen to 81 beats min^{-1}. Routine laboratory investigations revealed a full blood count within the normal range, urea and electrolytes: sodium 141 mmol litre^{-1}, potassium 4.6 mmol litre^{-1}, urea 7.4 mmol litre^{-1}, and creatinine 88 µmol litre^{-1}. The decison was made to proceed with surgery.

Following the placement of non-invasive monitoring and preoxygenation, anaesthesia was induced with thiopental 2.5 mg kg^{-1} and atracurium 0.5 mg kg^{-1}, with oxygen and nitrous oxide in a 50:50 ratio. Immediately, the heart rate rose to 165 beats min^{-1} with the ECG showing fast atrial fibrillation with concomitant ST-depression. The arterial pressure at this time was 156/84 mm Hg. A remifentanil infusion was commenced at a rate of 0.25 µg kg^{-1} min^{-1}. The heart rate slowed to 95 beats min^{-1} with an arterial pressure of 134/74 mm Hg; the ischaemic changes on the ECG also resolved. The heart rate remained stable at this level during subsequent laryngoscopy and intubation of the trachea. The patient received an infusion of magnesium sulphate 3 g intravenously. The remifentanil infusion was continued during the subsequent laparotomy with the rate adjusted according to the cardiovascular parameters. The patient remained in atrial fibrillation during the procedure and subsequent 24 h postoperatively in the HDU; however, there were no further episodes of fast artrial fibrillation.

The management of atrial fibrillation includes the use of drugs which slow A-V conduction, such as digoxin, verapamil and β-blockers.[2] The A-V node is innervated by both the sympathetic and the parasympathetic systems, the latter predominantly derived from the left vagus nerve.[3] Opioids lower the heart rate ablation of sympathetic tone and stimulation of the vagal nerve nucleus.[4] The increasing number of reports of remifentanil causing bradycardia[5] and asystole[1 6] suggest that it is particularly efficacious in this regard. It is likely that the remifentanil used in this setting slowed A-V conduction, causing the ventricular rate to drop to a more acceptable level.

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British Journal of Anaesthesia 88 (4): 615–18 (2002)

Book Reviews

Problems in Anaesthesia Series., L.A. Fleisher and D.S. Prough (editors-in-chief). *Perioperative Care of the Cardiopulmonary-Compromised Patient.* D. Nyhan (guest editor). Published by Lippincott, Williams and Wilkins, Philadelphia. Pp 269; indexed; illustrated. ISBN 0889 4698

This book focuses on the pathophysiological basis of right heart dysfunction and pulmonary hypertension in the perioperative context. In the preface, the guest editor affirms his objective, 'to provide the interested reader with one ready source of information mimimally redundant with existing material'.

The first section sets the scene with an in-depth consideration of the physiology of the pulmonary circulation and right ventricular function. Beginning with William Harvey's revelations of pulmonary blood flow in *De Motu Cordis* of 1628, Daniel Nyhan skilfully guides the reader through a summary of pulmonary vasoregulatory mechanisms, leading to the latest mechanisms of microvascular permeability. In the account of right ventricular function, the importance of aging in right ventricular dysfunction is emphasized.

The second section presents a series of wide-ranging perioperative problems, all of which contribute, in some degree, to disordered physiology of the pulmonary circulation and right ventricular function. The possible mechanisms of myocardial stunning are discussed in detail, and potential measures to alleviate this problem are discussed, especially choice of inotropes and ischaemic preconditioning.

The next two chapters focus on problems of heart and lung transplantation. Particular attention is paid to mechanisms underlying donor organ heart failure and potential therapeutic strategies to counter this problem. The role of ischaemia reperfusion in lung transplantation is considered at the mechanistic level and the deleterious implications for postoperative right heart function are described. The authors particularly highlight the need for development of techniques to predict differences in pulmonary blood flow and compliance, as well as vigilant monitoring of right ventricular function.

At this point, there is a change of theme to discuss the central importance of the pulmonary circulation in cyanotic and acyanotic congenital heart disease. The authors have achieved a balance between theoretical considerations affecting the perioperative pulmonary circulation, and a frank account of the practical management of these challenges. Extensive attention is given to practical management of the paediatric pulmonary hypertensive crisis.

One chapter is reserved for evaluating the role of echocardiographic assessment of the right ventricle. The authors acknowledge the limitation of this technique to precisely measure right ventricular dimensions and volumes but point to future refinements of three dimensional echocardiographic technology as holding promise for the future.

The final chapter considers the treatment options available for managing right ventricular failure. Beginning with a discussion of the relative merits and demerits of inotropes, the authors progress to a description of pulmonary artery balloon pump counterpulsation, extracorporeal membrane oxygenation, right to left shunts and right ventricular assist devices.

This book provides a refreshing analysis of the pathophysiology of pulmonary vascular and related right ventricular problems and does not fail to present the practical clinical implications of these issues. The contributors are to be congratulated on presenting a vast amount of well-referenced information in relatively small bounds. This volume is not for browsing. It requires a careful and detailed read to benefit from the wisdom therein. At times, the reader's task may have been assisted through more diagrams to illustrate some of the pathophysiology. Nevertheless, an attentive study of the text will compensate for this. I recommend this book, especially to all anaesthetists who retain an interest in the pathophysiology of the disease processes we grapple with every day.

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International Anesthesiology Clinics. W E Hurford (editor-in-chief). Vol. 39· Number 4. 2000. *Preoperative Cardiac Evaluation* K W. Park (editor). Published by Lippincott, Williams and Wilkins, Philadelphia. Pp. 108; indexed; illustrated. Price US$74. ISBN 0020-5907.

This slim volume *Preoperative Cardiac Evaluation* is a multi-author book produced in the standard format of International Anesthesiology Clinics. There are seven chapters by a variety of American authors. Dr Kyung W. Park, the Editor and Assitant Professor of Anaesthesia, Harvard Medical School, is an author or co-author of four of the chapters.

The first chapters provide a terse overview of non-invasive tests of myocardial perfusion and myocardial function. There is nothing new here for cardiovascular anaesthetists, but a good summary for those in general anaesthetic practice. The third chapter covers anaesthetic considerations for patients with cardiac arrhythmias, pacemakers and implantable defibrillators. This is a comprehensive chapter and, although the subject matter might be considered a little dull, the section on pacemakers and defibrillators is most useful.

The book is enlivened by the last four chapters. There is an excellent, and detailed, chapter on anaesthesia for adult patients with congenital heart disease undergoing non-cardiac surgery This is quite the best review we have read on this subject and is the highlight of the book The subsequent chapter on the future of the preoperative clinic is thought-provoking but less applicable to European practice.

The final two chapters provide a clinical review of the ACC/AHA guidelines for stratifying cardiac risk in patients undergoing non-cardiac surgery, and an overview of perioperative β-blockade in reducing cardiac risk. The former review on ACC/AHA guidelines is well written and informative. The chapter on β-blockade reviews the current literature on the subject, but concentrates on two papers by the groups of Mangano and Poldermans. It is interesting, but is limited in the respect that there are only seven references.

In summary, this is a book that would be useful to most UK anaesthetists who are likely to be exposed to a growing number of patients with cardiac risk factors For those who subscribe to International Anesthesiology Clinics, this volume represents good value. Individuals will probably not wish to pay US$74 for a single volume. The book would, however, be a welcome addition to any department library.

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Regional Nerve Blocks Textbook and Color Atlas 2nd Edn. D. Jankovic and C Wells. Published by Blackwell Science, Berlin. Pp. 340, indexed; illustrated. Price £99.50 ISBN 0 632 05557 X.

This book is in its second German edition and has been translated into this, the first English edition The intended readership is apparent from the Americanized spelling, although one of the authors is a senior UK anaesthetist. The book is well laid out and beautifully bound, as one would expect from Blackwells. The typeset and page size are the same as for this journal, providing adequate space for its abundant illustrations, which have the enviable clarity peculiar to digital photography. But Figures 4 16 and 4.17 are of doubtful illustrative value, depicting blurred images labelled 'blackout' and 'tonic-clonic seizures'.

As a colour atlas it soundly fulfils expectation though its standing as a textbook will take time to establish, set against numerous rivals already on the shelf. In his Foreword, Dr van Zundert claims there is a 'significant gap in the literature' concerning regional anaesthesia, which he predicts 'will be closed by this publication' Surely he must be referring to the German literature as there are a number of regional anaesthesia textbooks in the English language.

Techniques of somatic and autonomic nerve blockade are blended into clinical anaesthesia, obstetrics, postoperative analgesia and pain therapy in a logical sequence starting with the head and progressing down the upper body, thorax, abdomen, lower extremities and the neuraxis. There are a total of 430 international references, with some repeated including various textbooks. Occasionally the diction is didactic—there are a few 'nevers' and 'always'—which, no doubt, occurred in the original language Though these may not be out of place in a work practice guide or manual, such assurances are less enduring in the measured context of clinical wisdom—perhaps they might be softened in subsequent editions.

Some surprise omissions are: nerve block for ophthalmic surgery; penile block; and local anaesthesia of the larynx for fibreoptic inspection and tracheal intubation. Five pages are devoted to i.v. guanethidine block yet the more familiar i.v. regional block with local anaesthetic solution is neglected along with its eponymous originator, Bier. Diamorphine, still widely used, is not mentioned as a lipophilic contender for epidural administration, while fentanyl and of lesser UK relevance, sufentanil, are repeatedly recommended.

Each section covers a specific block and has a specimen recording chart and documentation form. The latter is comprehensive and could serve as an initial template for departments embarking on the use of separate documentation forms for local and general anaesthesia, assuming that the two might be mutually exclusive

Repetitive illustrations of materials for each nerve block could be condensed into a stand alone section, although it may have been the authors' original intention to have each nerve block as an independent section in the style of a working handbook. A chapter on sedation techniques in patients with regional nerve block would have been a useful addition and the recommendation of i.v. diazepam as a sedative, for inclusion in the emergency drugs kit, should be updated.

A brief introductory section describes basic local anaesthetic pharmacology, listing some specific agents in a formulary style including the LD50 mouse; the clinical relevance of the latter is questionable—its inclusion provides little meaningful therapeutic information.

The book is a good introduction to the subject; for more experienced anaesthetists, it provides easy revision for the application of nearly all types of nerve block. As an authoritative text and starting point to the literature it needs to mature through further English editions It is refreshing to see a volume of this magnitude attributable to only two authors; full credit to them for producing a useful teaching aid.

For £99, the committed anaesthetist who is learning local anaesthetic techniques for the first time would be making a good investment with the bonus of well illustrated anatomy. And, if FRCA examination candidates recognize the importance of embracing the concept of pain medicine as part of anaesthetic practice, they will reap the benefit of going through if from cover to cover.

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Imaging in Anaesthesia and Critical Care. Gregory Hobbs and Ravi Mahajan Published by Churchill Livingstone, London Pp. 182, indexed; illustrated. ISBN 0 4430 5310 3.

This book is a new title published in 2000. It has been written and edited by a combination of anaesthetists, radiologists and a physicist, mainly from Nottingham, UK. The book is targeted at trainees in anaesthesia and intensive care medicine. It is divided into six sections. *Basics of Imaging Techniques; Chest–Pulmonary Imaging; Chest–Cardiac Imaging; Head and Neck; Spine; and Abdomen and Pelvis.*

The chapter on *Basics of Imaging Techniques* is very good; it provides a sensible, concise summary, sufficient for the purpose of the book. We did, however, try to determine differences between spinal CT and CT from reading this chapter, but this was not covered

The section on the *Chest–Pulmonary Imaging* is probably the area of most interest to the intended readers of this book. It provides an excellent review of the subject Most common problems are covered, and it is eminently suitable for FRCA preparation A minor criticism would be that there is very little detail or illustration of the use of ultasound of detecting pleural collections, which is increasingly used in the intensive care setting, on occasions solely by anaesthestists. We also feel that there could have been more detail about detecting all the various catheter misplacements that occur e.g. nasogastric tubes in the bronchi, and the various misplacements of venous access devices. Regrettably, if one has never seen these abnormalities on x-ray film, it is all too easy to miss them in the clinical setting.

The chapter on *Chest–Cardiac Imaging* is a comprehensive account of this area. There is a very good explanation of applied radiological anatomy. Again it is very suitable for FRCA candidates. We were surprised to see no mention of the use of ultrasound guidance for vascular access anywhere in the book, as this is an area where anaesthetists actually use ultrasound on a regular basis.

The sections on *Head and Neck*, and *Spine Imaging* occupy nearly half the book, and there is possibly more detail in these chapters than that required by the presumed readership. It is questionable just how much detail individual anaesthetists need or would retain in these areas. Those working in trauma or neurointensive care would perhaps find this detail of value. The chapter on *Abdomen and Pelvis Imaging* provides a good, short summary. The images shown will be helpful for interpretation of plain abdominal films in the intensive care setting.

Overall, we would recommend this book to trainees and consultants It is very well suited for FRCA preparation. In our view, it is the cardiac and chest images that are most important. These are the images that the intended readership are expected to interpret personally without formal radiology reporting

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Top Tips in Critical Care. G.R. Park and R.N. Sladen (editors). Published by Greenwich Medical Media Ltd., London. Pp. 154. Price £12.50. ISBN 1 84110 120 6.

Top Tips in Critical Care is a small volume which is edited by G.R. Park from Addenbrookes Hospital, Cambridge, and R.N Sladen from Columbia University, USA. It contains contributions from 32 practitioners from all over the world.

The book is aimed at a wide readership of critical care specialists both in training and in practice—nurses, anaesthetists, operating department practitioners, and other professionals involved in the care of critically ill patients, for example physiotherapists. It aims to provide a list of useful 'tips' (how to do something), and 'caveats' (how not to do something). These tips and caveats are grouped into 15 chapters, covering a variety of areas in the management of the critically ill patient, including airway management and artificial ventilation, through to guidance with the insertion of pulmonary artery catheters, and problems with sedation and nutrition

Many of the tips and caveats provided are small pieces of advice or information that are passed on from one colleague to another over the course of time; they are the useful tips that make patient management so much easier. Examples include drugs to avoid in asthmatic patients, or how to detect hypovolaemia from the arterial waveform. Another simple set of guidelines that could prove useful are on obtaining the optimum level of PEEP in the artificially ventilated patient.

Some of the tips can help to explain why the patient is behaving in an unexpected manner, when all is not going according to plan. Examples include an easy-to-follow method for calculating and checking drug doses in $\mu g\,kg^{-1}\,min^{-1}$, and a reminder that if the patient develops tachyarrhythimas shortly after starting inotropes, they are probably underfilled.

The editors freely admit that much of the advice given is against the trend of evidence-based medicine; it is much more anecdotal in nature with the points mentioned, in many cases, being too small to warrant publication. Although experienced practitioners will find that they have heard of many of the tips and caveats, there is certainly a lot of useful information for the less experienced, more junior practitioner. There are also clear instructions for carrying out various practical procedures, such as the measurement of intra-abdominal pressure, performing an ascitic tap, and central venous cannulation. Some of the tips may be viewed as not entirely orthodox by some clinicians; it may be advisable for juniors to discuss with their senior colleagues before trying some of the manoeuvres suggested, such as using a beta agonist to correct hyperkalaemia, or a combination of hydrochlorthiazide, human albumin and high dose frusemide to correct oliguria in patients with a low glomerular filtration rate

The book is written in a very readable style It is well laid out with a clear list of contents at the beginning, and chapter contents at the start of each chapter. The size of the book is such that it will fit into a pocket or rucksack, making it easy to carry around and to refer to at the bedside on the intensive care unit. It complements many of the larger textbooks in that the information given is practical, rather than theoretical in nature.

In summary, this is an interesting, readable, cheap and useful little volume which will appeal to a fairly wide readership. Its size and style will certainly make it a useful starting point at the bedside, when inspiration is needed on to how to manage a patient. A second collection of *Top Tips* will be awaited with interest.

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Acute Pain Management, A Practical Guide. 2nd Edn. P.E. Macintyre and L.B. Ready. Published by W.B. Saunders. Pp 258; indexed; illustrated. Price £22.95 ISBN 0 70202581 X.

It is an indication of the growing importance, awareness and progress in the field of acute pain management that the first edition of this little book, published in 1996, has already been revised and three new chapters added. It is written by P.E. Macintyre, Director of the Acute Pain Service at The Royal Adelaide Hospital, Australia, and L B. Ready, Director of The University of Washington Medical Centre Pain Service, USA. The book is aimed at a number of health care professionals, from junior doctors and trainee anaesthetists, to ward nurses and specialist pain nurses. It attempts to bridge the gap between the anatomy and physiology of acute pain, which is often well understood, and the practical aspects of managing patients on the ward, which are frequently practised poorly.

The authors clearly have a wealth of knowledge and experience which they bring to this book in a digestible and informative manner. The second edition comprises 12 chapters, following the addition of those dealing with potentially difficult clinical problems such as *The Opioid Dependent Patient, Acute Neuropathic Pain*, and *The Elderly Patient*. All the chapters are written by the two authors. The introductory chapter provides persuasive evidence of why acute pain management is now regarded as important ethically, and how good pain management can impact favourably upon patient outcome following majar surgery

When addressing a target readership with a wide variety of knowledge of the clinical sciences, it is often difficult to strike the right note in terms of detail. The authors admirably manage to provide a concise and readable account of, for example, the pharmacology of the opioids. The adverse effects of opioids are dealt with well, important advice is given, for instance, on how respiratory rate is a late indicator of respiratory depression, and how supplemental oxygen therapy may mask it. I suspect junior medical and nursing staff on the ward will find the book useful in dispelling some of the myths of patient-controlled analgesia, as the authors state, 'An inadequate understanding of PCA . . . at best [it] can prove to be a very expensive way of providing suboptimal analgesia'. Trainee anaesthetists will find the book of use in preparing for postgraduate qualifications in anaesthesia.

The text is generously illustrated with text boxes and figures. The text boxes make good use of bullets which emphasize important points made in the main text, and are an aid to quick referencing on the wards. Of particular help, I suspect, will be the examples of worked calculations. These aids are made use of abundantly in the chapter on the opioid-dependent patient, where a patient-controlled analgesia regimen is calculated based on patients' usual daily requirements of various opioid preparations (both prescribed and illicit)

In the appendices to the chapters on patient-controlled analgesia and epidural analgesia, are examples of standard physician prescription sheets, nursing standing orders, and observation charts in use at the authors' institutions. Physicians designing an acute pain service in their own hospitals may find these documents valuable

The three new chapters are interesting and useful. Neuropathic pain is explained well and examples given of how this underdiagnosed condition may be encountered in the postoperative setting; both commonly recognized causes such as limb amputation, thoracotomy and mastectomy, and less well known causes such as third degree burns are discussed The chapter on the elderly patient is well structured and provides important information on how opioid prescribing may need to be modified, especially in respect of patient-controlled analgesia, in this age group.

My criticisms of the book are few. Regarding epidural analgesia, I was slightly disappointed not to read more of the evidence for the positive effects of this method of analgesia on patient outcome. Large meta-analyses have been published in recent years on this topic, but the authors cite only one reference to postoperative pulmonary outcomes at the end of the chapter.

I would also have liked to read more about the practical aspects of acute pain management in the paediatric population as junior medical staff sometimes have responsibility for children. This is, however, an increasingly specialist area.

Overall, junior medical staff on the wards, nurses, and anaesthetic trainees will find this book most useful. It is small, lightweight, and easily portable. While it may not be suitable for every trainee in anaesthesia to own a copy, I would recommend that every anaesthetic department keep one in their library.

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British Journal of Anaesthesia **88** (4): 619 (2002)

Erratum

General versus *regional anaesthesia for hip fracture surgery: a meta-analysis of randomized trials (BJA 2000; 84: 450–5)*

The Peto OR values in Table 2 should have been centred around 1 and not 0 as printed. The publishers apologize for this error.

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Guide to Contributors

The purpose of the *British Journal of Anaesthesia* is the publication of original work in all branches of anaesthesia, including the application of basic sciences. One issue each year deals mainly with material of postgraduate educational value.

Papers for publication and all editorial communications should be addressed to: Prof. J. M. Hunter, Editor-in-Chief, *British Journal of Anaesthesia*, University Department of Anaesthesia, Royal Liverpool University Hospital, The Duncan Building, Daulby Street, Liverpool L69 3GA, UK. Tel./Fax: +44 (0) 151 706 4005. E-mail: bja@liv.ac.uk

Papers

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Preparation of manuscript

Four copies of each manuscript (including revised texts) should be submitted and should indicate the title of the paper, the name(s), full address(es) of the author(s), and be in letter quality heavy type (not dot matrix), double-spaced on one side only of the paper, with a wide margin. Contributors should retain a copy in order to check proofs and in case of loss. Where possible, manuscripts should also be submitted on disk. Our preferred format is a 3.5″ PC floppy disk with the file written in Word 6 for Windows. However, it is also possible to process disks submitted in other formats, provided sufficient information is supplied to enable conversion to the preferred format. Articles on disk should be prepared in the simplest possible form. Please do not use endnotes, footnotes, etc. for references. Correct fonts, type sizes, column measures, etc, will be added by the technical editor.

Each of the four copies submitted must be accompanied by a complete set of figures. One set of figures must be unmounted glossy prints (see below); the three other sets may be photocopies.

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Papers in recent issues of *British Journal of Anaesthesia* should be consulted for general and detailed presentation. They are most often subdivided into:

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Discussion
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Summary

The summary will be printed at the beginning of the paper. It should be on a separate sheet, in structured format (Background; Methods; Results; and Conclusions) for all original articles (Clinical Investigations, Laboratory

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Three to five key words or phrases (for indexing) should be included below the summary.

Introduction

The introduction should give a concise account of the background of the problem and the object of the investigation. Previous work should be quoted only if it has a direct bearing on the present problem.

Methods

Methods must be described in sufficient detail to allow the investigation to be interpreted and repeated by the reader. Any modification of previously published methods should be described and the reference given. If the methods are commonly used, only a reference to the original source is required.

Drugs

When a drug is first mentioned it should be given the international non-proprietary name, followed in parentheses by the chemical formula only if the structure is not well known, and by the capitalized proprietary name.

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Monographs:

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485 Cerebral Hyperemia, Systemic Hypertension, and Perioperative Intracranial Morbidity

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488 Rapacuronium and Pediatric Bronchospasm
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500 Low Pressure CO_2 Pneumoperitoneum in Children, ScO_2, and Cerebral Blood Volume
506 Correlation of the BIS Monitor in the Pediatric ICU
512 Tension Pneumothorax in a Newborn (Case Report)

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(Society of Cardiovascular Anesthesiologists)

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523 Tramadol Infusion for Postthoracotomy Pain
529 Leukocyte-Depleted Packed Red Blood Cells and Postoperative Infections
538 Pharmacokinetics and Pharmacodynamics of Hextend®
545 Direct Myocardial Effects of Xenon
552 Ketamine Suppresses Norepinephrine-Induced IP_3
558 Left Ventricular Outflow Tract Obstruction Complicating Lung Transplantation (Case Report)

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560 Fast-Tracking Geriatric Outpatients
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569 Sevoflurane Anesthesia and Physostigmine
573 Succinylcholine and Outpatient Anesthesia (Brief Report)
577 Non-Opioid Analgesics and Postoperative Pain (Review Article)

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(Society for Technology in Anesthesia)

586 Cerebral Oxygen Saturation
591 Neuromuscular Transmission Module for Neuromuscular Block Monitoring

ANESTHETIC PHARMACOLOGY
(International Society for Anaesthetic Pharmacology)

597 Potency of Muscle Relaxants at Acetylcholine Receptors
604 Propofol and Mivacurium Are Not Synergistic
609 Awakening Propofol and Clonidine Concentrations
615 Clonidine Blunts Stress Response to Tourniquet
619 Effects of Tramadol on Renal Blood Flow
626 Thermoregulatory Effects of Urapidil
631 2N Suppresses Fear Conditioning

ECONOMICS AND HEALTH SYSTEMS RESEARCH

640 Data Requirements for Operating Room Staffing
644 Outpatient Preoperative Evaluation

NEUROSURGICAL ANESTHESIA

650 Cerebral Hyperemia During Recovery
655 Effects of Thiopental and Propofol on Cell Swelling
661 Cerebral Blood Volume/Cerebral Blood Flow in Tumors During Isoflurane or Propofol
667 Tracheal Intubation in Cervical Spine Disorders
672 Extravasation Injury by Intravenous Phenytoin (Case Report)

OBSTETRIC ANESTHESIA

674 Primary Action of Epidural Fentanyl is Spinal
680 Spinal Ropivacaine for Cesarean Delivery
686 Rocuronium in Postpartum Patients (Brief Report)
690 Parturients and Alternative Medicine (Special Article)

PAIN MEDICINE

694 Spinal Cord Stimulation in Postherpetic Neuralgia
701 Adjuvant Induced Inflammation and Spinal Amino Acid Release

REGIONAL ANESTHESIA

706 Ultrasound and Psoas Compartment Block
711 Prolonged Antinociceptive Nerve Block with 5% Butamben
717 Test Dose Efficacy and Propofol
723 Regional Anesthesia, Sedation Scale
729 Bacterial Growth in Ropivacaine (Brief Report)

GENERAL ARTICLES

732 Morbid Obesity and Tracheal Intubation
737 ProSeal™ Laryngeal Mask Airway in Obese Patients
741 Anesthetized Obese Respiratory Mechanics
749 Tropisetron and Postoperative Nausea and Vomiting
754 Latex Allergy Desensitization
759 The "SLIPA™" Single Use Airway Device (Brief Report)
762 LETTERS TO THE EDITOR
769 BOOK AND MULTIMEDIA REVIEWS

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